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# REAL-WORLD OUTCOMES ASSOCIATED WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) THERAPIES FOR PATIENTS TREATED IN THE UNITED STATES VETERANS HEALTH ADMINISTRATION SYSTEM

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**by**

**Obiageri Obodozie-Ofoegbu**

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# Dedication

DEDICATED TO THE LORD GOD ALMIGHTY, FOR HIS STEADFAST LOVE THAT NEVER CEASES. YOU ALONE OH LORD KNOWS THE COST OF MY ALABASTER BOX. YOUR PRAISE WILL CONTINUALLY BE IN MY MOUTH.

Fear not, for I am with you; be not dismayed, for I am your God; I will strengthen you, I will help you, I will uphold you with my righteous right hand.
~ Isaiah 41:10. (KJV)

**And**

*To the Memory of my father, Chief Nathaniel Eboro Ekwu, who inspired and encouraged me to never give up on my dreams.*

***"Change can be scary, but you know what is scarier? Allowing fear to stop you from growing, evolving, and progressing."***

- *Mandy Hale*

## Acknowledgements

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I appreciate Xavier Jones for all his work with obtaining the data from VHA databases and all he's taught me in data processing. I equally thank my co-graduate student Eric Teng and all past and present P3 PharmD students whom I have had the pleasure to work with under Dr. Frei's supervision especially Alyssa Castillo who was of tremendous and reliable help during the summer months of 2020 working on this project, despite the Covid-19 pandemic. My colleagues past and present in the graduate school (Andrea Chen, Kristina, Shiraz, Stefan, Amina, Eric Young, Bret, Sam, James and Cody), some of whom have become personal friends, I thank God for the opportunity to have met each one of you. Thanking Giovanni, Char Burke, Laura Patterson, Melissa, George, Johnny and Susan for all their help and friendship. All the Faculty of PERC and College of Pharmacy, UT Austin

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# Abstract

**Title: Real-world outcomes associated with Chronic Lymphocytic Leukemia (CLL) therapies for patients treated in the United States Veterans Health Administration System**

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Background: Chronic lymphocytic leukemia is the most predominant leukemia of all the hematologic malignancies. It disproportionately afflicts older male Caucasians. It is classically considered a manageable but incurable disease. Consequent upon diagnosis, several treatment options are available, and the choice of which to use is determined to a large extent by the clinical, biological, and genetic manifestations of the disease.

Up until 2014, gold standard for CLL treatment was chemoimmunotherapy-based. The advent of targeted therapy with agents that function at the gateway of dysregulated enzyme pathways, completely transformed the CLL treatment arena. The last decade has witnessed shifts in paradigm and rapidly changing treatment practices, attendant upon several new drug/treatment approvals. What type of shift in uptake and volume of the various classes of CLL agents has occurred due to these changes in pattern.?

Our study set to determine the shift in therapies of nine CLL therapies in the Veterans Health Administration System. It described the pharmacoepidemiology of traditional chemotherapies/chemoimmunotherapies (CT/CIT) and the novel agents, in the VHA CLL is a highly variable disease with important patient contributed factors that can affect outcome. Our study also focused on outcomes associated with these therapies, with a view to determining which are important influencers.

This was a retrospective study of adults with CLL in the VHA from 10/01/2013 to 5/31/2018. All were followed for at least 6 months. Data were extracted from the VHA electronic health record. Patients came from all 18 Veterans Integrated Service Networks, spanning all 50 states and US territories. Descriptive statistics were used to summarize the data, and chi and student-t-test to compare drug use, outcomes, and complications. Statistical significance was accepted at $P<0.05$.

Our study showed that a total of 1,456 patients across all lines of therapy received at least one of nine CLL therapies of interest. Patients had a median age of 70 years (76% were 65+ and 24% were <65 years). A median age-adjusted Charlson comorbidity score of 5, and 9% had a history of exposure to Agent Orange. Within the period studied, CT/CIT accounted for about 73% of all treatments, while the novel agents use was 27%. Ibrutinib was predominantly used in first and second lines of therapy. Ibrutinib use across all lines of therapy (LOTs) increased steadily while traditional CT/CIT use declined steadily over the study period. However, the traditional chemoimmunotherapies were predominantly used in patients under 65 years old, while ibrutinib was used more on those older than 74 years. A non-significant but higher incidence of diffuse large B cell lymphoma post-index

was higher in patients on CT/CIT than those on ibrutinib. Concomitant use of some medications increased the relative risk of death for both the novel agents and the CT/CITs but was seen more with the latter.

In conclusion, novel agents are transforming the CLL treatment landscape, Traditional chemoimmunotherapies are still important in a subset of CLL patients. There has been a major shift in the treatment of CLL, with fast adoption of novel agents in the VHA from 2013 to 2018.

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## GLOSSARY

| Acronym | Meaning |
|---|---|
| AE | Adverse Event |
| ASCO | American Society of Clinical Oncology |
| ASH | American Society of Hematology |
| B2M | Beta2-Microglobulin |
| BCL-2 | B-cell lymphoma 2 |
| BCR | B-cell Receptor |
| BH3 | Bcl – Homology 3 |
| BR | Bendamustine and Rituximab |
| BTK | Bruton's Tyrosine Kinase |
| CAM | Complementary and Alternative Medicine |
| CAR-T | Chimeric Antigen Receptor T-cell |
| CD | Cluster of Differentiation |
| CT/CIT | Chemotherapy /Chemoimmunotherapy |
| CLL | Chronic Lymphocytic Leukemia |
| CML | Chronic Myeloid Leukemia |
| COPD | Chronic Obstructive Pulmonary Disease |
| CR | Complete Response |
| Del (17p) | 17p Deletion |
| DFS | Disease Free Survival |

| | |
|---|---|
| DLBCL | Diffuse Large B-Cell Lymphoma |
| DUR | Duration of Response |
| EHR | Electronic Health Record |
| EMR | Electronic Medical Record |
| FCR | Fludarabine, Cyclophosphamide, Rituximab |
| FDA | Food and Drug Administration |
| FISH | Fluorescence In Situ Hybridization |
| FY | Fiscal Year |
| HR | Hazard Ratio |
| Ibr (IBR) | Ibrutinib |
| ICD-9-CM | International Classification of Diseases, 9th Revision, Clinical Modification |
| ICD-10-CM | International Classification of Diseases, 10th Revision, Clinical Modification |
| IwCLL | International Workshop on CLL |
| MAB | Monoclonal Antibodies |
| MRD | Minimal or Measurable Residual Disease |
| OR | Odds Ratio |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PCR | Polymerase Chain Reaction |

| | |
|---|---|
| PFS | Progression Free Survival |
| PI3K | Phosphoinositide 3-kinase |
| PPI | Proton Pump Inhibitor |
| R | Rituximab |
| RCT | Randomized Controlled Trial |
| R/R | Relapsed/Refractory |
| RT | Richter's Transformation |
| SLL | Small Lymphocytic Lymphoma |
| TKI | Tyrosine Kinase Inhibitors |
| TLS | Tumor Lysis Syndrome |
| TTNT | Time to Next Treatment |
| US | United States |
| VA | Veterans Affairs |
| VHA | Veterans Health Administration |
| VenR | Venetoclax-Rituximab |
| Ven (VEN) | Venetoclax |
| WHO | World Health Organization |

# CHAPTER ONE

# LITERATURE REVIEW

## OVERVIEW OF CHRONIC LYMPHOCYTIC LEUKEMIA

### *What is chronic lymphocytic leukemia?*

Leukemia, cancer of the white blood cells, is one of the most common types of blood cancer.[1] It is myeloid or lymphoid in origin and comprises four biologically distinct subgroups of hematopoietic malignancies, viz. acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia and chronic myeloid leukemia. It is acute when it shows up in the precursor cells and chronic when it manifests in the mature cells.[2] Leukemia represents the 10th most common cause of cancer deaths and 11$^{th}$ most common cause of cancer incidence worldwide.[3] According to the WHO classification of Tumors of the Hematopoietic and Lymphoid Tissues, chronic lymphocytic leukemia (CLL) is a low-grade lymphoproliferative neoplasm, with $\geq 5x10^9$/L circulating clonal B-cells that express CD5, CD19, CD20, CD23.[4] CLL is the most prevalent leukemia in adults in the Western world, and it accounts for 25% to 30% of all leukemia types.[5, 6] It is a blood and bone marrow disease where the body makes excessive amounts of lymphocytes that do not work properly because their DNA is damaged and cannot fight infections appropriately, negatively impacting the body's immune system. It has been described as an "accumulation of functionally incompetent lymphocytes."[7] It is a slow-growing disease and sufferers may be symptomless for several years. While some patients have a rapidly progressive disease that requires treatment, others may never

require therapy due to a very indolent clinical course of their disease. The disease typically affects older people and is rare in those aged < 50 years.[8] Only about 6% of sufferers are aged below 50 years, while 25% are aged below 65 years at diagnosis.[9] Today CLL disease remains incurable, therefore treatment goal remains palliative, to slow down disease progression and prolong life. In recent years, due to large improvements in treatment options and the availability of targeted therapeutic and combination agents, 5-year survival has increased to over 66%, from 60% in the past decade, with over 80% of treated patients alive at 3 years.[6] The economic burden of CLL in the United States is currently about $0.74 billion, projected to rise to $5.3 billion by the year 2025. This almost 600% increase in 6 years is mostly attributable to the entrance of the oral targeted therapies, which are considerably more expensive than the traditional therapies.

***Epidemiology of Chronic Lymphocytic Leukemia***

Globally, about 191,000 cases and 61,000 deaths due to CLL are recorded yearly. The incidence of CLL has been found to differ among different races and geographic locations, however, race rather than geography has been found to have more impact[10] Higher incidence rates are associated with countries in which human development index is high, including Canada, Australia, United States of America, and several European nations; whereas lowest incidence rates are found in West Africa and Asia.[11] The incidence rate was 4.83/100,000 people in the United States from 1975 to 2014, with current estimates of about 20,000 new cases expected each year and an estimated 130,000 people currently living with the disease.[3] CLL is more common in whites than in blacks,

very rare among Asians, and almost twice more likely to affect males than females. [12,13] In 2019, 20720 new cases have so far been recorded in the United States, comprising 12880 males and 7840 females.[14] Improved health care and better lifestyles translate to an ever-aging population, and therefore, the median age at the diagnosis for CLL has increased from 65 years in the early 1990s,[15,16] to 70-72 years in the present day.[10]

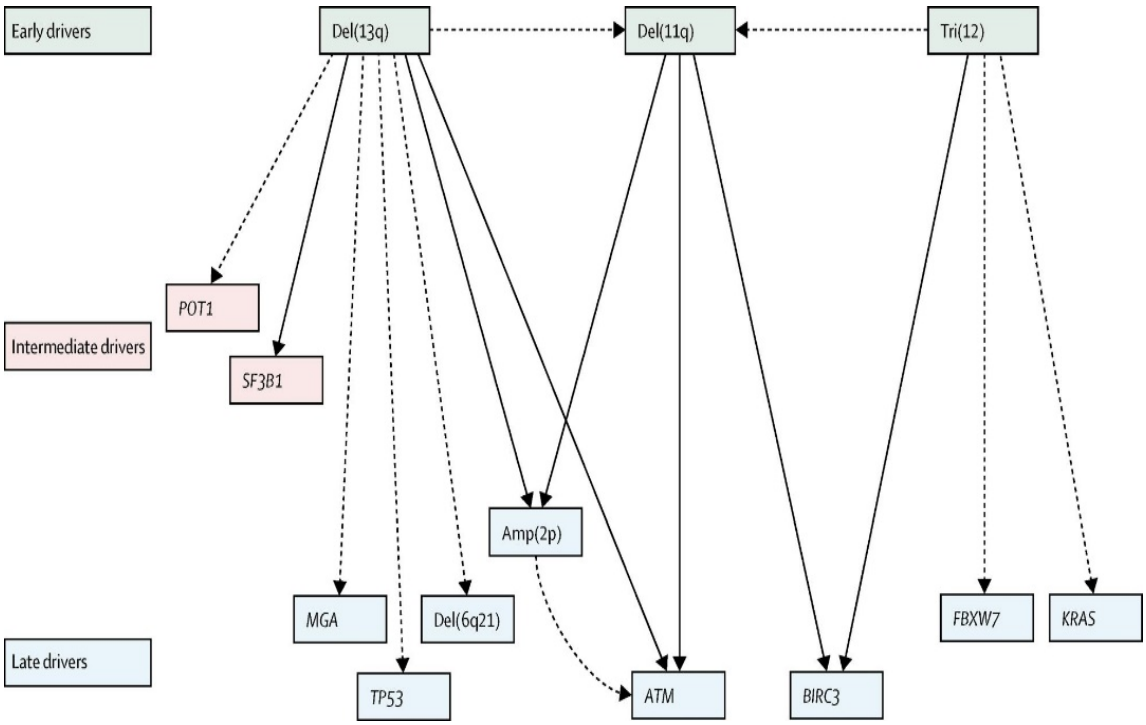



**Figure 1.1** Genetic Drivers of CLL *(Source: (REF27) Hallek et al 2018)*

***Diagnosis and Prognosis in CLL***

Diagnosing CLL is often incidental, due to the nature of the disease to be asymptomatic for long periods. Patients present with an abnormally high white blood cell count (>5000 monoclonal lymphocytes/$mm^3$), which may be accidentally discovered during routine blood count for a different condition. CLL is the most common cancer cause of unexplained high absolute lymphocyte count, although only a count of >5000/ $mm^3$ may be indicative of CLL, the presence of greater than 5000/$mm^3$ clonal B-cells in peripheral blood is required for diagnosis. Clonality of the B-cells confirmed by flowcytometry is required for establishing diagnosis. CD19, CD20, and CD23 are normal antigens expressed by B-lymphocyte, however, the presence of CD5, an antigen commonly expressed by T cells, but not B-cells is confirmatory of CLL.[27] Other clinical presentations at diagnosis include lymphadenopathy which occurs in about 50%-90% of patients at time of diagnosis, cytopenias (autoimmune thrombocytopenia, autoimmune neutropenia, autoimmune hemolytic anemia) may be less frequently seen. Fever, night sweats, weight loss, and fatigue may not be present at this stage. Fingerprinting the lymphocytes to prove that they are all clonal and consistent with B-cell chronic lymphocytic leukemia is among the minimum requirements that must be met before a diagnosis of CLL is confirmed, in order to avoid exposing patients to misdiagnosis, inappropriate prognosis and wrong therapy.

**CLL Staging Systems and Prediction Tools**

Two staging systems are commonly used for the characterization of CLL for prognosis and treatment purposes. The Rai staging system established in 1975, used more in the United States, was formerly a 5-stage system but was revised in 2016 into a risk stratified system that divides patients into low risk (Rai stage 0), intermediate risk (Rai stages I and II), and high risk (Rai stages III and IV).[28] The stratification in the Rai system is based on lymphocytosis and other clinical features. The Binet system used more in Europe, was established in 1977 has three stages A, B, C. The classification is based more on number of involved areas, head and neck, axillae, liver spleen and groins as well as the presence of lymphadenopathy hemoglobin levels, and platelet levels.[29] Current developments in CLL therapy and molecular characteristics have rendered these two staging systems largely insufficient in identifying all risk groups in CLL.[30]

A description of features of the Rai and Binet staging systems are summarized in Table 1.1.

| **STAGE** | **CLINICAL FEATURES** | |
|---|---|---|
| | **RAI System** | **Binet System** |
| **Low risk (stage 0), A** | Lymphocytosis in the blood and bone marrow only | Hb ≥ 10g/dl, Platelets ≥ 100x109/L, < 3 lymph node areas involved |
| | | |
| **Intermediate risk (stages I and II), B** | Lymphocytosis + enlarged nodes at any site or enlarged spleen or enlarged liver | As in stage A, in addition to ≥ 3 lymph node involved. |
| | | |
| **High risk (stages III and IV), C** | Lymphocytosis + Hb < 11g/dL or platelets < 100 x 109/L | HB < 10g/dL or Platelets < 100x109/L |

**Table 1.1** Rai and Binet Staging Systems

Due to the heterogenic nature of CLL disease, both staging systems fall short in their ability to be predictive of disease progression because they do not consider other prognostic factors such as genetic aberrations that can also impact risk stratification and disease progression. For example, the clinical course of CLL in patients is more benign if they have a mutated immunoglobulin heavy-chain (IGHV), while 17p deletion is associated more with aggressive disease.

Scientists have developed different prognostic models predictive of time to first treatment and prognosis.[31] Some of these models have been found to help with improving clinical information useful in supporting the management of CLL, while the use of others has been limited by complexity and the need for information that are not easily available. The international prognostic index, a CLL prognostic scoring index (CLL-IPI), has been validated and shown to be a highly reproducible and effective prognostic tool for predicting OS. It is the most relevant prognostic tool currently. It was developed using a weighted combination of five independent prognostic factors namely, age, clinical staging, IGHV mutational status, $\beta_2$-microglobulin concentration and TP53 status. The tool stratified patients into four risk groups (low, intermediate, high, and very high), with distinctly different five year-overall survival.[32] It proposes different treatment strategies for the different risk groups.

CLL is a slow-growing disease, and about 25%-30% of patients will not require treatment at the time of diagnosis, while others will need some form of treatment.[33] Typically, patients in the Rai low risk stage or Binet A are usually carefully observed

without any treatment until rapid disease progression or they become symptomatic. The time to first treatment (TTFT) is an important parameter in newly diagnosed CLL patients because it can impact overall survival (OS). TTFT and treatment type are mainly determined by patient and disease-related variables, such as the aggressiveness of an individual's disease, a patient's functional status, co-morbidities, and the biology of the disease. Prognostic models, such as the CLL International Prognostic Index (CLL-IPI), that use a weighted combination of prognostic markers like age, clinical stage, TP53 status and TP53 mutation, serum beta2 microglobulin, and IGHV mutation status, typically have been used to predict survival in CLL patients. The CLL-IPI stratifies patients into four distinct risk groups (low, intermediate, high and very high risk), with significantly different overall survival (OS), based on a scores index.

The investigators who developed the CLL-IPI demonstrated that this type of prognostication index can be useful in predicting TTFT, including those newly diagnosed patients who are in the 'watch & wait' category. [32] They found that depending on the risk group, the TTFT differed. They were able to validate the number of patients that will commence CLL treatment for each year following diagnosis for up to 10 years post diagnosis in three cohorts. By year 5 of diagnosis, 10-25% of low risk, 46-71% of intermediate risk, 68-80% of high risk and 75-100% of very high-risk patients had initiated treatment. When analyzed in the cohort irrespective of risk group, 25-35% of the 'watch& wait' patients commenced treatment by the fifth year of diagnosis. This analysis is supported by published studies reporting that 60-70% of previously untreated patients

with CLL with traditional clinical and laboratory features remained treatment-free at 60 months of diagnosis.[34]

### *Pharmacotherapy of Chronic Lymphocytic Leukemia*

CLL is regarded as a slow-growing and incurable disease for which some patients may never require treatment, while others eventually will need some form of therapy. [32,35] Following the diagnosis of CLL in an individual, careful risk assessment is essential to select appropriate treatment. For most patients, their disease is early stage and they are not usually offered immediate treatment but managed with close observation and surveillance to identify when to initiate treatment upon disease progression. About 70% of such patients end up requiring treatment.[36] Call Generally, there is no one-size-fits-all therapy; rather, the landscape is quite diverse with several options. Important factors in making treatment decisions are not limited to the clinical staging of the disease, and the evaluation of disease-specific prognostic biomarkers such as genetic anomalies, but also depend on age, comorbidities, physical capacity, nutritional status, cognitive capacity, ability to perform activities of daily living, social support and more recently, cost of treatment.[37] Real-world data are still emerging from on-going studies as regards the treatment options in terms of tolerability, adverse effects, long term use, and disease outcome.[38]

CLL therapies continue to evolve, leading to changing treatment paradigm. Three distinct phases in the advancement of CLL therapies can be clearly identified. For a long time, chlorambucil, with or without a steroid, was the only therapy available for CLL

patients who required treatment. Survival after treatment initiation was typically about five years, with complete remission in about 5%, and progression-free-survival of about one year. The first major therapeutic advancement was the purine analogues (fludarabine, pentostatin, and cladribine) in the 1980s. They were effective against chemotherapy-resistant CLL.[39,40] Next, was the addition of the anti-CD20 antibodies. Which began with a human-murine chimeric antibody, rituximab. The demonstration of modest clinical activity of rituximab, an antibody targeting the B-cell surface phosphoprotein CD20 as a single agent, marked the beginning of the immunochemotherapy era for CLL. It was found effective as a single agent in doses that are higher than are typically administered in other B-cell lymphomas.[41] Presently, there are ample studies to demonstrate that the addition of an antibody to chemotherapy for CLL patients achieves a better outcome than with chemotherapy alone. Anti-CD20 antibodies are a group of compounds that are added to chemotherapy regimens to provide a patient with chemoimmunotherapy (CIT). The anti-CD 20 antibodies used in CLL therapy include rituximab, obinutuzumab, and ofatumumab. The combination of fludarabine, cyclophosphamide, and rituximab (FCR) was the first CIT regimen to prolong the OS of CLL patients. [43,29] Other combination treatments with these immunotherapies include: bendamustine plus rituximab (BR), pentostatin plus cyclophosphamide plus rituximab (PCR), ofatumumab plus chlorambucil (O+CB), obinutuzumab plus fludarabine plus cyclophosphamide (G+FC), obinutuzumab plus bendamustine (GB).[443,0] Several studies have shown these to be treatment options that have improved outcomes for CLL patients to varying degrees.[45,46] For a long time, FCR was the standard of care for first-line treatment of fit CLL patients, having been

shown effective in an MD Anderson Cancer Center (MDACC) study, with long-term outcomes of 72% complete response rate and 95% overall response rate. [47,48] BR is also another CIT that has a comparable outcome to FCR and is widely used in community settings. [49] In some cases, the immunotherapeutic agents have also been used as monotherapies as maintenance treatment regimens in some patients. Historically, therefore, we moved from single-agent therapy to treatment guidelines where chemotherapy, with the addition of an antibody, were the foremost regimens in the management of CLL. The goal of chemoimmunotherapy was disease eradication because their therapeutic mechanism targets the pathogenic cause of CLL by the elimination of the malignant B-cell clones, achieving high minimal residual disease (MRD) negativity and high clinical response rates. They are usually used in single or multiple cycles of treatment with a finite course or duration.

As knowledge in the molecular biology and roles of prognostic factors in the clinical presentation of CLL continues to grow, novel targeted therapies; the B-cell receptor (BCR) inhibitors and B-cell lymphoma 2 (BCL-2) inhibitors that function at the checkpoints of dysregulated enzyme pathways have emerged. They have recently become the focus in CLL therapy, both as first-line treatments and in refractory/relapse cases. Ibrutinib, a Bruton tyrosine kinase inhibitor (BKI), was the first such agent to be approved by the FDA in 2013 for the treatment of mantle cell lymphoma and in February 2014, its approval was expanded to include its use in treating CLL patients who have received at least one previous therapy.[50,51] Others are idelalisib (phosphatidylinositol 3-kinase inhibitor),[52] and venetoclax, a Bcl-2 inhibitor,[53,39] approved for patients with

relapse and del (17p). The use of ibrutinib is rapidly becoming standard of care as first-line therapy for weaker older treatment-naive CLL patients,[55,56] patients with poor-risk cytogenetics and decreasing fitness, as well as in relapsed cases. [57,58] The goal of therapy with these agents is disease control through sustained preservation of response and amelioration of disease symptoms. This way, they maintain enduring response and achieve long progression free survival (PFS). These agents are used to treat until progression or death occurs and their treatment course remains indefinite.

With the advent of newer therapies, and the marked efficacy they have shown in clinical trials, the role of CIT is changing, with a generally downward trend. However, there is a need for cautious optimism, because the oldest of the targeted therapies, ibrutinib, has been used for less than ten years and scientists still have much to learn about this therapy. In addition, patients who are more physically fit and have better prognostic factors might still be good candidates for the chemoimmunotherapies. This is more so when one considers the adverse reactions, treatment discontinuation, drug resistance, high cost of treatment, and indefinite treatment regimens associated with the novel agents.

Recently, CLL regimens based on combination strategies using agents from different classes and different mechanisms of action, are being evaluated and pushed into practice, in effort to improve depth of response, time-limited treatment duration, adherence, as well as reduce treatment failures, and improve patient outcomes. While combinations of CIT and targeted agent plus anti-CD20 antibodies have been in use for over two decades, double targeted agents with or without anti-CD20 antibodies are

becoming the next paradigm shift in CLL management. A pictorial summary of the time-line of CLL therapies evolvement is shown in figure 1.2.

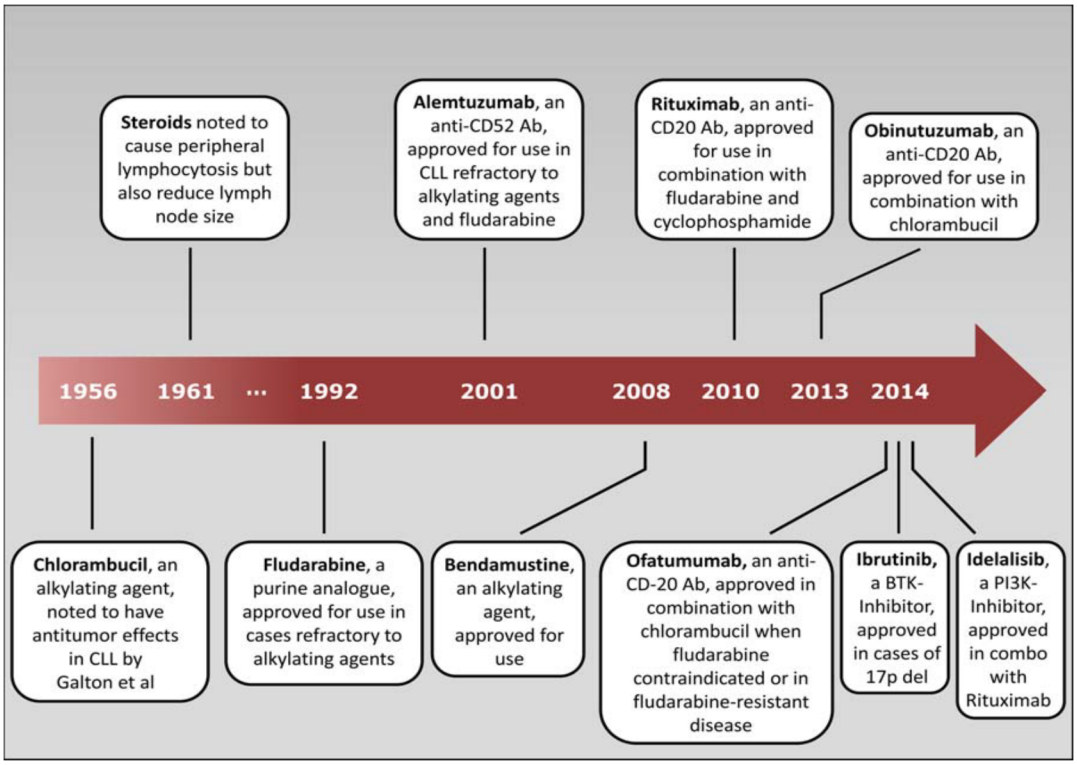



**Figure 1.2.** Timeline highlighting historical therapeutic milestones and recent FDA approvals in CLL drug development. Ab=antibody, RR=relapsed refractory.
*Source: Mato et al 2015 (REF59)*

### *Mechanisms of action of CLL agents*

The importance of understanding the way a drug elicits its effect is crucial in making appropriate choice of agent and finds relevance in the sequencing of therapies in CLL, considering that most people will require a series of agents over time.[60,61] It helps guide the decision whether to use these agents as sequential monotherapies or

combinations. Some of the anti-CLL agents have direct cytotoxic effect on the cancer cells and pathways, while others such as lenalidomide are immunomodulatory, and work at the level of the microenvironment and immune system. Currently, 4 to 5 major mechanisms are available for use in the drug treatment of CLL. Chlorambucil, bendamustine, and cyclophosphamide are alkylating agents that target and cause damage in cancer cells by inducing DNA inter strand crosslinks. The nucleoside analogues (purine analogs) such as fludarabine, pentostatin, and cladribine inhibit enzymes relevant in DNA synthesis. Fludarabine inhibits the function of the DNA polymerase enzyme, primase, while pentostatin and cladribine inhibit adenosine deaminase required for DNA processing. Therefore, a combination of alkylating agents and purine analogues will induce DNA damage and inability of repair to occur, resulting in better killing effect on cancer cells. [62,63]

Anti-monoclonal CD20 antibodies are immunotherapeutic agents that target the overexpression of phosphoprotein CD20 on the surface of B-cell lymphoma cells. They attach to the surface of the cell by virtue of the CD20. Rituximab, Obinutuzumab, ofatumumab and Alemtuzumab (anti-CD52) have all been tried as maintenance chemotherapeutic agents alone or used in various combination regimens in CLL. Rituximab was the first of the anti CD20 to be approved by the FDA in 1998. Its modes of action consist of mainly cell-mediated cytotoxicity and direct apoptosis to a lesser extent.[64] Obinutuzumab is a genetically engineered anti-CD20 that combines both anti CD20 and immunoglobulin monoclonal antibody. Upon binding to CD20, it also induces complement-mediated cell death and apoptosis which are both actin reorganization-

dependent and lysosome-mediated.[65] It has been shown to elicit the most potent response of the class. Ofatumumab, a humanized anti-CD20 targets a different epitope from rituximab for its action on complement-mediated cell-death and apoptosis. The anti-CD20 agents oftentimes produce better overall survival and response as components of combination therapies with other class agents than when used as sequential monotherapies, because they are mostly effective for treating indolent lymphomas. Historically, they were used in combination regimens with the purine analogues and alkylating agents but are now in new use as combination agents with the targeted therapies.[66,67]

Lenalidomide is an immunomodulator that induces immune effector T and NK cells as well as other cancer targets. It is a thalidomide analogue that down regulates cytokines thereby producing anti-angiogenic effects. Among its many anti-cancer mechanisms, is the upregulation of some anti-tumor genes and proteins leading to erythroid progenitor proliferation and cell adhesion in the cell microenvironment. Its optimal use in CLL management is still being evaluated due to its multiple mechanisms of action, toxicities and cross-toxicity with other agents. However, it shows some promising synergies with idelalisib and anti-CD20 agents

The B-Cell Receptor (BCR) pathway is critical for B-cell development, survival, and migration. Ibrutinib, the first of the BCR-inhibitors to be approved for use in CLL, is an irreversible BTK inhibitor.[68] It binds covalently to the cysteine 481 in the active site of the Bruton Kinase enzyme, this reduces further downstream signaling of other enzymes specific for the cellular responses to cytokines in the cancer pathway. This action hinders

the migration and proliferation of cancer cells.[69] In other words, the BTK inhibitors inhibit the pathways for stimulus for the cell to live. Idelalisib and duvelisib are inhibitors of phosphatidylinositol 3-kinases (PI3K). Approved in 2014 by both the FDA and European Medicines Agency (EMA) for use in relapse/refractory CLL, idelalisib selectively inhibits PI3Kδ, while duvelisib inhibits isoforms PI3K-δ,γ.[70]

The inhibition of PI3Kδ induces apoptosis in cell lines derived from B cell malignancies by promoting the inhibition of proliferation, chemotaxis, motility, adhesion, and survival of B cell. [58] Inhibition of both isoforms yields greater activity.[71] Venetoclax is an oral B cell lymphoma 2 (BCL2) inhibitor pro-apoptotic agent, targeting the antiapoptotic protein BCL-2.[72] It is a BH3 mimetic that can cause immediate apoptosis of tumor cells by triggering and executing self-death in the cells. BH3 mimetics bind to the B-cell hydrophobic groove, inducing apoptosis and venetoclax can selectively target BCL2. Of all the novel agents, only venetoclax has been shown to produce deep, durable remissions.[73]

CLL treatment strategies involving combinations of agents with different modes of action are rapidly gaining grounds in both practice and experimental settings. For example, the combination of ibrutinib plus venetoclax, two drugs with different mechanisms of action has recently been given initial license due to the synergistic action shown in efficacy by the doublet. Preclinical studies in man and animal models show that BTK inhibitors increase the sensitivity of CLL cells to BCL-2 inhibitors.[74,75] Ibrutinib induces lymphocytosis that depletes the lymph nodes of tumor cells and mobilizes them into peripheral blood while venetoclax induces apoptosis that occurs

mainly in the blood and bone marrow, therefore both efficacies complement each other.[76,74] Other combinatorial regimens are also being tested; BR + Obinutuzumab and venetoclax, where BR is expected to initially debulk the tumor, followed sequentially by time-limited maintenance regimen using Obinutuzumab+ venetoclax.[77] Also, trial testing ventetoclax+ibrutinib and Obinutuzumab, alongside other four treatment regimens including the chemoimmunotherapy FCR/BR in physically fit patients is on-going.[78]

Currently, response to treatment is assessed to be one of the following, complete remission, partial remission, stable disease, refractory disease and progression. Recently a new response criteria 'minimal residual disease' negativity has been added as an increasingly important response because recent studies have shown that MRD in patients who achieve complete or partial response can predict better progression free survival (PFS).[79,80]

**Review of critical literature on RCTs that established important management therapies.**

Randomized controlled trials have often played key roles in determining safety and efficacy of outcomes of therapies. In CLL arena, many of such trials have focused on evaluating new ways of treating the disease and improving outcome. Many landmark clinical trials have changed the course of CLL treatment. A brief review is shown in table 1.2.

| Study/ Authors/year | Objective | Study Design | Population | Interventions / Trial Arms | Outcome | Comments |
|---|---|---|---|---|---|---|
| CLL8<br><br>[47]Keating et al -2005 | To evaluate if FCR increases CR in treatment naïve patients | Single arm study of FCR as initial therapy. MRD was measured | 224 patients, median age 58yrs | FCR | FCR produced high CR rate [(70%) (95% CI, 63% to 76%)] and overall response rate of 95% (95% CI, 92% to 98%). | FCR was shown to produce high response rate in treatment-naïve patients |
| [27]Hallek et al 2010 | Evaluate whether the inclusion of anti CD20 will improve outcome for CLL patients | Prospective RCT (open label, phase 3). 1:1 ratio of two intervention arms (FCR vs FC). | 817 Treatment naïve patients, (aged 30–81 years) | FCR vs FC Endpoints: PFS and OS | FCR improved PFS 65% vs 45% (hazard ratio 0·56 [95% CI 0·46–0·69], p<0·0001) and OS 87% vs 83% alive ((0·67 [0·48–0·92]; p=0·01) | This established FCR as standard of care for CLL in fit patients |
| [81]Fischer et al, 2012 | Evaluated efficacy of BR in treatment naïve patients | Nonrandomized multicenter phase II study | 117 patients ≥18yrs enrolled. | BR only. Primary endpoint: ORR, toxicity, MRD, event-free survival, quality and duration of response. | Median age: 64years (34 -78), ORR was 88.0% (95% CI, 80.7% to 100.0%; n = 103) | Established BR regimen in treatment-naïve CLL patients. |
| [49]CLL10 trial. Eichhorst et al, 2016 | Compared efficacy and tolerability of FCR with BR. | Open-label, randomized, phase 3, non-inferiority trial | 561 treatment-naïve patients aged 33-81 years | FCR vs BR. Endpoint: PFS, OS, ORR, MRD | Median progression-free survival was 41·7 months (95% CI 34·9–45·3) with BR and 55·2 months (95% CI not evaluable) with FCR (HR 1·643, 90·4% CI 1·308–2·064). Toxicities and complications more with FCR arm. | Null hypothesis of non-inferiority not rejected. FCR remains standard frontline therapy in fit patients but BR is less toxic. |

**Table 1.2** Select Practice-changing Clinical Trials in CLL Therapy (Abbreviations: ACAL, acalabrutinib; BR, bendamustine + rituximab; CLB, chlorambucil; CLL, chronic lymphocytic anemia; FCR, fludarabine, cyclophosphamide and rituximab; FC, fludarabine, cyclophosphamide; G, obinutuzumab; IBR, ibrutinib; R, rituximab; O, Ofatumumab; VEN, venetoclax; IDEL, Idelalisib)

| Study/ Authors/year | Objective | Study Design | Population | Interventions / Trial Arms | Outcome | Comments |
|---|---|---|---|---|---|---|
| Thompson et al, 2016 | To determine if there were patients who achieved DFS following first-line therapy with FCR | As described in CLL 8 trial. Relapse and survival data continued to be collected. MRD was determined for survivors with highly sensitive flow cytometry | Long term follow-up of 72 surviving patients CLL8 study. A 12.8 years follow-up. | As described in CLL 8. Only long-term survivors were accessed. | MRD-negativity predicted superior long-term survival in patients with *IGHV-M* only; 12.8-year survival was 87.2% vs 56.5% for MRD-negative and MRD-positive patients, respectively (*P* = .003). Median PFS was not reached (NR) for patients with *IGHV-M* and 4.2 years for patients with *IGHV-UM* (*P* < .001). 12.8-year PFS was 53.9% for patients with *IGHV-M* and 8.9% for patients with *IGHV-UM*. | Natural history of CLL on those receiving the gold standard therapy (FCR) Emergence of a plateau at 10.4 years without any relapse for survivors, indicating a possible 'cure'. |
| [50]Resonate Byrd et al 2014 | Evaluated efficacy of ibrutinib in relapsed / refractory CLL | Multicenter open-label phase 3 RCT | 391 patients with relapsed or refractory CLL or SLL | IBR vs O. Endpoint: PFS, OS and CR rate | Median PFS 9.4months for ibrutinib vs 8.1 months for ofatumumab, overall response rate was (42.6% vs. 4.1%, P<0.001) in favor of Ibr. OS was better for IBR, (HR, 0.43; P<0.005) | Ibrutinib significantly superior to ofatumumab in improving PFS, OS and response rate in RR CLL patients Included del(17p) and purine analogue resistant patients |
| [55]Resonate-2 Burger et al 2015 | To compare two oral agents in treatment-naïve CLL or SLL patients. | International open-label phase 3 RCT | 269 treatment naïve CLL or SLL ≥65yrs, no del(17p), median age = 73yrs | Ibrutinib vs chlorambucil. Endpoint: PFS | Ibrutinib overwhelmingly superior to chlorambucil in PFS, (median not reached vs 18.9 months, risk of progression to death 84% lower in ibrutinib (HR, 0.16; P<0.001) and OS at 2yrs was 98% vs 85% in favor of ibrutinib (HR, 0.16; P<0.001); overall response rate = 85% vs 35%, P<0.001 in favor of ibrutinib | Showed overall advantage in OS with targeted agent |

**Table 1.2(CONTD)** Select Practice-changing Clinical Trials in CLL Therapy (Abbreviations: ACAL, acalabrutinib; BR, bendamustine + rituximab; CLB, chlorambucil; CLL, chronic lymphocytic anemia; FCR, fludarabine, cyclophosphamide and rituximab; FC, fludarabine, cyclophosphamide; G, obinutuzumab; IBR, ibrutinib; R, rituximab; O, Ofatumumab; VEN, venetoclax; IDEL, Idelalisib)

| Study/ Authors/year | Objective | Study Design | Population | Interventions / Trial Arms | Outcome | Comments |
|---|---|---|---|---|---|---|
| [52]Furman et al 2014 | Efficacy and safety of Idelalisib in combination with rituximab in RR CLL patients | A Multicenter double-blind, placebo-controlled phase-3 RCT | 220 patients with decreased renal function, preexisting comorbiditie s, therapy-induced myelosuppre ssion | IDEL + R vs R + placebo. Endpoint: PFS | PFS was superior for idelalisib (not reached) vs 5.5 months in the placebo group (hazard ratio for disease progression or death in the idelalisib group, 0.15; P<0.001). OS was better for idelalisib (92% vs. 80%; hazard ratio for death, 0.28; P=0.02). Idelalisib had improved OR 81% vs 13% for placebo (odds ratio, 29.92; P<0.001) | Established the use of idelalisib - rituximab in patients who are not able to undergo chemotherapy |
| [83]CLL 11 Goede et al 2014 | Can chlorambucil be beaten, does Obinutuzuma b confer any advantage over rituximab | Multinational randomized phase 3 trial. Three study arms with a safety run-in phase. Includes direct comparison of Anti CD 20-based arms with CLB alone. | 256 Older patients with comorbiditie s Used 256 patients for primary endpoint and 633 for secondary endpoint | CLB + G vs CLB vs CLB + R | Anti CD20 + Chlorambucil was superior in PFS, TTNT, ORR, OS. Chlorambucil + Obinutuzumab was better in long term follow-up over than rituximab +Chlorambucil for PFS and OS | Changed practice to use of Chlorambucil + Obinutuzumab in elderly patients with comorbidities |
| [84]ECOG-E1912 Shanafelt et al 2019 | Efficacy of Ibrutinib + rituximab compared with standard chemoimmun otherapy | 2:1 comparison of FCR given in standard dosing and IBR +R. FCR, IBR given in 6 cycles, then IBR monotherapy until disease progression. | 529 patients ≤70yrs (median age 57 and 58), no del(17p), no prior therapy randomized in a 2:1 ratio of FCR or IBR + R. Patients stratified to 2 age groups (≤60years vs 60-70 years) | FCR vs IBR + R Endpoint: PFS disease progression or death | IBR + R was superior in PFS and OS. PFS favored IBR (89.4% vs. 72.9% at 3 years; HR for progression or death, 0.35; 95% [CI], 0.22 to 0.56; P<0.001) 65% reduction in risk of disease progression or death with Ibrutinib and OS advantage for ibrutinib 98% vs 91 (HR for death =0.17; 95% CI .05-0.54; p<0.003) | Established Ibrutinib-based therapy as most effective for untreated CLL. Patients were generally younger and fit. Paradigm shift for treatment-naïve younger patients. Impact in IGHV-mutated disease was similar in both groups (HR=0.44; 95% CI 0.14-1.36; p=0.07). FDA approval for IBR+R use in younger treatment naïve patients. |

**Table 1.2(CONTD)** Select Practice-changing Clinical Trials in CLL Therapy (Abbreviations: ACAL, acalabrutinib; BR, bendamustine + rituximab; CLB, chlorambucil; CLL, chronic lymphocytic anemia; FCR, fludarabine, cyclophosphamide and rituximab; FC, fludarabine, cyclophosphamide; G, obinutuzumab; IBR, ibrutinib; R, rituximab; O, Ofatumumab; VEN, venetoclax; IDEL, Idelalisib)

| Study/ Authors/year | Objective | Study Design | Population | Interventions / Trial Arms | Outcome | Comments |
|---|---|---|---|---|---|---|
| [85]ALLIANCE A041202 Woyach et al 2018 | To determine whether the addition of rituximab to iburutinib yields better outcomes than ibrutinib alone in older patients. | Phase 3 clinical trial. Patients were randomized to one of 3 study arms in a 1:1:1 ratio. | 547 treatment-naive patients aged ≥65 years (median age, 71 years) | BR vs IBR vs IBR + R. Endpoints: PFS, OS, CR and MRD | IBR-based therapy was better in PFS but no clear advantage of combining it with rituximab. No significant difference in OS between the interventions. | Single agent IBR recommended as frontline therapy for older patients. |
| [86]MURANO TRIAL. Seymour et al, 2018 | To evaluate the efficacy of venetoclax + rituximab in relapsed or refractory CLL patients | Randomized, open-label, phase 3 trial. Not a crossover study | 389 relapsed patients age ≥18years, median age was 65 years (range, 22-85) randomized into either of 2 arms. | VEN+R vs BR. Endpoint: PFS | PFS and OS were longer with VEN+R across all biologic and clinical sub-groups. 2-year rates of progression-free survival were 84.9% and 36.3%, respectively (hazard ratio for progression or death, 0.17; 95% confidence interval [CI], 0.11 to 0.25; P<0.001 by the stratified log-rank test). | Benefit of venetoclax plus rituximab over bendamustine plus rituximab was established. Benefit was also seen in patients with 17p deletion. FDA approved this combination for use in previously treated CLL patients |
| [73]CLL14 Fischer et al 2019 | To test the efficacy of venetoclax/obinutuzumab | Randomized, open-label, phase 3 trial. | 445 treatment-naïve patients with comorbiditie s (CIRS >6 and/or creatinine clearance <70mL/min | CLB + G vs VEN + G Endpoint: PFS, safety | PFS at 24 months was significantly higher in the venetoclax–obinutuzumab group than in the chlorambucil – obinutuzumab group: 88.2% (95% CI, 83.7 to 92.6) as compared with 64.1% (95% CI, 57.4 to 70.8). No significant difference in all-cause mortality between both arms. | A critical study that led to Venetoclax + obinutuzumab being approved by FDA for 1L treatment of CLL patients with comorbidities. |

**Table 1.2(CONTD)** Select Practice-changing Clinical Trials in CLL Therapy (Abbreviations: ACAL, acalabrutinib; BR, bendamustine + rituximab; CLB, chlorambucil; CLL, chronic lymphocytic anemia; FCR, fludarabine, cyclophosphamide and rituximab; FC, fludarabine, cyclophosphamide; G, obinutuzumab; IBR, ibrutinib; R, rituximab; O, Ofatumumab; VEN, venetoclax; IDEL, Idelalisib)

***Other on-going RCTs of note include:***

FLAIR[87] - In a phase 3 trial by the United Kingdom group (the FLAIR trial), treatment-naïve patients with CLL are randomized to 1 of 4 treatment arms: (1) FCR, (2) ibrutinib + rituximab, (3) ibrutinib, and (4) ibrutinib + venetoclax.

CLL 13[88] - In a phase 3 trial by the GCLLSG (the CLL13 trial), treatment-naïve patients with CLL are randomized to 1 of 4 treatment arms: (1) FCR/BR (based on age younger than or equal to 65 or older than 65 years), (2) venetoclax + obinutuzumab, (3) venetoclax + rituximab, and (4) venetoclax + ibrutinib + obinutuzumab.

***CLL Treatment Protocols and Guidelines***

CLL disease is considerably benign in the earlier years, becomes more progressive and resistant during the last few years. Typically, overall survival (OS) is 5-10 years, within which time, patients may die of progressive disease or complications of therapy. However, a few patients with aggressive disease die within the first 2-3 years following diagnosis.[28,89,45] It is important to note that CLL therapy is currently a moving target, with ever constantly changing scene. In the last eight years, development and standard of care for CLL has been rapidly evolving and official guidelines that define treatment guidelines, response to therapy, and clinical assessment are changing accordingly. The goal of therapy is to improve outcome by prolonging progression free survival and minimizing adverse effects of treatment. Current perspectives in treatment

paradigms revolve around continuous indefinite therapy and fixed course duration with sequential combination of agents.

Changes in treatment guidelines have also been occurring as new knowledge on the disease and its treatment emerge. The National Comprehensive Cancer Network,[90] the European Society for Medical Oncology Guidelines for CLL[91] and the International workshop on CLL criteria are guidelines that are recently being used to define diagnosis, treatment and clinical response.[92]

For low and intermediate risk patients with no symptomatic disease, a "wait and watch" approach is recommended. It has been shown that there is little or no benefit in initiating treatment early.[93,94,95] Initiating therapy for the first time is left for active or symptomatic disease determined by the International Workshop on CLL criteria.[92] When initiating therapy, treatment choice is guided by patient-based characteristics including comorbidities, age, and drug toxicity, this is the first line of therapy. Newly diagnosed patients with high-risk features of the disease can benefit from early intervention through clinical trials.[96] It is important to note that CIT has no role where there is P53 gene aberration but will rather increase risk for complications. For younger and physically fit patients without *TP53 (P53 aberration or del17p)* anomaly, FCR is used as the standard of care, otherwise, ibrutinib is recommended. The CLL8 study demonstrated that 68% of patients treated with FCR were alive at 5.9 years of observation, and for patients with IGHV-mutated disease, the median progression-free survival exceeded 96 months at end of follow-up. Toxicities associated with FCR include neutropenias and increased risks of

infections. Substituting fludarabine with bendamustine or pentostatin, or reducing the dose of FCR, tend to be equally potent, but less toxic.[81,97,98]

Chlorambucil with or without steroid is used mainly for elderly, frail patients, and with patients who have comorbidities, irrespective of age. Addition of anti-CD20 to chlorambucil improves OS when compared with chlorambucil alone. For treatment-naïve patients, in whom FCR might be considered inappropriate, ofatumumab plus chlorambucil is indicated. In recent times, the addition of obinutuzumab to chlorambucil is considered more adequate for elderly patients with comorbidities.[83] It is also indicated in relapsed cases in patients who had previously received fludarabine-based therapy. Sometimes, the anti-CD20 can be extended as monotherapy for maintenance therapy, where the disease has become progressive. [99]

The newer therapies that target dysregulated pathways (ibrutinib, idelalisib, and venetoclax) have greatly increased treatment options for CLL, improved outcomes and consequently changed a lot of what guidelines existed prior to 2015. Ibrutinib is used as first line therapy in frail elderly patients, patients with 17p deletion (a more aggressive disease), patients with unmutated IGHV-status, and relapse cases. In situations where ibrutinib is not suitable due to the presence of certain comorbidities or adverse co-medications, idelalisb plus rituximab, or venetoclax, have been shown to improve response rates, PFS, and OS.[52] Ibrutinib is also largely used as initially approved, in relapsed / refractory CLL [55,58] It is now indicated in every CLL and widely prescribed. Venetoclax was initially approved for CLL patients with del17p, but currently it is the treatment of choice after ibrutinib failure as indicated by clinical trial that showed up to

70% response rate in patients who received venetoclax after ibrutinib.[100] Recent approval of venetoclax+obinutuzumab for use in treatment naïve patients following the outcomes of the CLL14 clinical trial, brings it into first line use.[101]The targeted therapies currently available are orally administered and are taken for as long as they remain effective or interrupted by adverse effects, drug resistance, and emergent comorbidities. Ibrutinib has a high tendency to cause bleeding and atrial fibrillation; therefore, its use in patients with a history of cardiac disease and bleeding disorders is given careful consideration. Compromised immune systems and opportunistic infections may also limit the use of some of the newer therapies.

Pharmacotherapeutic management of CLL disease continues to be the focus of research studies. Since the newer therapies hardly achieve complete remission in patients, they are taken until adverse effects or disease progression occludes their continued use. Recent studies have demonstrated promising results in looking to fashion therapies with individualized approach by combining the novel therapies with chemoimmunotherapies, especially in patients with severe disease. The principle in this approach is to initially reduce the high tumor burden in severe disease with a CIT agent, then apply novel agents and monoclonal antibodies for the induction and maintenance phases.[102] Current practices seem to suggest that chemotherapy and chemoimmunotherapy is no longer the primary agent in CLL management for many patients, standard practice is now in favor of single-agent treatments, doublets, and potentially, triplets of novel agents. Treatment protocols are now moving towards novel combinations as more knowledge become available, for example, the CLARITY trial that evaluated combination of BTK inhibitor (ibrutinib plus

a BCL-2 inhibitor (venetoclax) without anti-CD20 antibody.[88] Similarly, the Eastern Cooperative Oncology Group (ECOG) is also conducting a three-drug combination regimen that adds Obinutuzumab to ibrutinib and venetoclax.[103]

The future is still unfolding for CLL therapies—one that may see the use of current therapies in an approach that combines their different molecular mechanisms specifically customized to suit each patient's needs.

| **Therapy** | | **Regimen (Days)** | **Cycle Interval (Days** | **No of Cycles** |
|---|---|---|---|---|
| Fludarabine + Cyclophosphamide + Rituximab | FCR | 1-3 | 28 | 6 |
| Fludarabine + Rituximab | FR | F: 1 - 5<br>R: 1 & 4 | 28 | 6 |
| Pentostatin + Cyclophosphamide + Rituximab | PCR | 1 | 21 | 6 |
| Bendamustine + Rituximab | BR | B: 1<br>R: 1-2 | 28 | 6 |
| Alemtuzumab | | 1, 2, 3 or 5 (3 times/week) | 7 | 12 |
| Chlorambucil | Chlorambucil (monotherapy) | 1<br>1-5<br>1 /daily | 28<br>28<br>28 | 12 (max) or until disease progression |
| Chlorambucil + Obinutuzumab | Chlorambucil + CD20 | As above +<br>O: 1,2,8,15 | 28 | 6 |
| Chlorambucil + Prednisone | | C: 1<br>Pred: 1-5 | | |

**Table 1.3.** CLL Therapies Protocols

| Therapy | | Regimen (Days) | Cycle Interval (Days | No of Cycles |
|---|---|---|---|---|
| Chlorambucil + Ofatumumab | Chlorambucil + CD20 | C: as above Ofa: 1 &8 for cycle 1, then higher dose on day 1 for minimum of 3 cycles | 28<br>28 | 12<br><3 and >12 |
| Chlorambucil + Rituximab | Chlorambucil + CD20 | C: 1-7<br>R: Day 3 in cycles 3-8; then continue maintenance therapy of 1<br><br>OR<br><br>C: 1-7<br>R: 1 | 28<br><br><br><br><br>56 (q8wk)<br><br>28 | 8<br>6<br><br><br><br><br>For 2yrs<br><br>12<br>12 |
| Ofatumumab | CD20 (monotherapy) | 1,8,42<br>then continue<br>1 | 42<br><br>56 (q8wk) | 1<br><br>2 years max |
| Ibrutinib | Ibrutinib (monotherapy) | daily | N/A | Until unacceptable toxicity or disease progression |
| Idelalisib (may be in combination with Rituximab) | | daily | 1 | |
| Duvelisib | | daily | | |
| Lenalidomide | | daily | 21 | Indefinite |
| Lenalidomide + Rituximab | | L; as above<br>R: weekly (cycles 1&2)<br>Monthly (cycles 3-12 | 21<br>21 | 12<br>12 |
| Venetoclax | | daily | | Until unacceptable toxicity or disease progression |

**Table 1.3(CONTD)** CLL Therapies Protocols

***Drivers of Treatment Patterns and Outcomes in Real-world CLL Management***

Historically, the approach to the clinical management of CLL has been based more on risk stratification using the Rai and Binet staging which are dependent on CBC and lymphadenopathies. In recent times, algorithms that are more inclusive of prognostic molecular markers such as TP53 deletion, IGHV-mutation status, serum b2-microglobulin, whose presence or absence impact disease severity, prognosis, and outcome, are increasingly being used to determine treatment.[32] The interplay of these prognosticating factors with other host factors, such as comorbidities, age, and frailty can chart the course of the clinical management of CLL and influence treatment best practices. This has become more important since the introduction of the targeted therapies because cytogenetics, comorbidities and/or co-medications, weigh in more, in the decision, and the choice of which targeted agent to use. A plethora of treatment regimens (mono and combo regimens) are becoming more available for CLL management across all lines of therapy (LOT) and the novel agents have proven to offer better responses than CIT in the relapsed setting.[47,104]

Predictably, patterns of care for CLL patients changed in response to the entrance and availability of the targeted agents due to the remarkable advances in improving clinical outcomes and durable responses they elicited in multiple CLL studies. Consequently, the last decade has witnessed shifts in paradigm with rapidly changing treatment practices and treatment guidelines, as well as several new drug/treatment approvals driven by these agents.[105] Ibrutinib, the first of the novel agents to be approved, currently has 11 indications since its approval in 2013, including indications for treating

most patients in both first line and relapsed settings, as monotherapy and in combination with anti CD20 monoclonal antibody agents. Despite the impressive impact of the newer agents, unique toxicities and cost of treatment associated with them pose a challenge and continue to present significant differences between them and CIT.[106] Furthermore, recent studies have noted differences between real-world data and the clinical trial reports, in the use of the targeted therapies.[107]

What changes in uptake and volume of the various CLL therapeutic agents have occurred since the introduction of the targeted therapies? From 1999 to 2015, Bendamustine/Rituximab (BR), Fludarabine/Cyclophosphamide/Rituximab (FCR) and chlorambucil have each been reported to be the most common regimen used, followed by rituximab alone as the second most common regimen across all lines of therapy.[108, 109,110] It is notable that despite the existence of treatment guidelines, different studies conducted within similar time periods from various practice settings have reported differences in treatment uptake. Differences could arise due to other contributory factors besides age, patient's functional health status, comorbidities, clinical and biological manifestations of the disease, which are significant considerations in the choice of therapy. Such factors include differences in practice settings, physician experience/choice, and factors related to patient-choice including quality of life, financial burden, and serious adverse effects. These have been shown to be tangible drivers of treatment patterns. [111,110,112] Patients prefer treatment regimens that offer longer PFS, however, they are willing to accept significant tradeoffs for it, to avoid serious adverse events.[113]

The novel agents are not cheap, cost of treatment is a potential issue for many patients. Recent studies have shown that the introduction of these therapies has substantially increased the cost of CLL treatment from both the payer and patient perspectives.[25,65] Yearly cost of most of the novel agents such as ibrutinib is more than twice the annual income of an average American family with an out-of-pocket cost of about $36,000, compared to a CIT cost of only $325 in some cases.[114] One study showed that per patient lifetime treatment cost increased from $147,000 to $604,000. In addition, the incremental cost-effectiveness ratio, when compared with chemoimmunotherapy, stands at $189,000 per Quality Adjusted Life Year (QALY).[115] This clearly is a cost scenario that could potentially constitute a serious financial burden to most patients, which in turn, can lead to a poorer outcome in the real world, due to lack of affordability and consequent treatment discontinuation. Reports in literature indicate that higher out-of-pocket costs for cancer treatments have been associated with non-compliance and lack of adherence among cancer patients.[116,117] Therefore, despite the clinical activity and widespread use of these newer agents as frontline therapies, not all patients can use them.

***Treatment Complications and Adverse Effects***

Major safety concerns with CLL therapies as with other cancer therapies are treatment-related toxicities and adverse effects. It is critical in CLL therapy that patients are monitored for toxicities and adverse effects, so that they may be caught early and the necessary interventions made to forestall treatment disruptions and maximize outcomes, despite the challenging adverse effects. Common toxicities associated with the CIT such

as FCR are grade 3-4 neutropenias (about 34% of patients) and infections (about 25% of patients).[43] To mitigate this level of toxicity, attempts to create less toxic but equally potent regimen led to the use of reduced doses of FCR, or replacement of fludarabine with pentostatin or cladribine or Bendamustine in the FCR combo. These were similarly toxic or less effective as FCR.[118,119,120,121,81] The German CLL10 trial reported that although the FCR patients had longer median PFS than BR patients, there were equally more patients in this group that had severe grade neutropenias and infections.[49] Ibrutinib has greater toxicities that differ from those of chemotherapies and these treatment-related toxicities have been associated with frequent discontinuation of the agent in real world, a phenomenon seen more with older (>80 years) and frail (worse ECOG performance) patients.[122]It has three times the risk of developing atrial fibrillation.[123] while the use of PI3K inhibitors like idelalisib has been associated with immune-mediated adverse events like transaminitis, colitis, severe viral and pneumocystis infections, which seem to be more common when these agents are used in the first line setting. [124,125] It is recommended therefore that patients on these agents be given prophylaxis against pneumocystis jirovecii pneumonia (PJP) and be closely monitored for cytomegalovirus (CMV) reactivation, where there's prior history of the infection.[126,127] Venetoclax safety concern is related to its ability to elicit tumor lysis syndrome (TLS).

***Comorbidities in the treatment of CLL***

CLL primarily affects older people. The median age at diagnosis is about 72 years with over 70% of new cases being 65 years and above.[9] Most elderly persons are living

with one or more comorbidities and some level of receding organ function.[128] Comorbidities play a major role in the selection of therapy in CLL management and literature reports that a high percentage of CLL patients have a comparatively greater comorbidity burden than their younger counterparts.[129] The presence of these comorbidities may affect their biological status, rendering them 'fit' or 'unfit'. Due to the fact that the elderly come with different 'fit' levels, the traditional approach of using chronological age for therapy selection may be flawed because patients of same age but with different fit status will most likely respond differently to a particular therapy. Therefore, it has become a recommended practice to assess biological rather than chronological age using the burden of comorbidities and 'fit' status.[130]

Literature reports have given contrasting results on the impact of comorbidities on CLL outcomes.[131] probably due to the different performance measurement indices used to determine the burden of comorbidities.[132] Measures used to determine performance status include Eastern Cooperative Oncology Group[133] and the Karnofski performance scale. Often used along is the estimation of comorbidity burden using Charlson comorbidity index,[134] and Cumulative Illness Rating Scale.[135] Classification of patients as fit or unfit is based on their renal function (unfit when the glomerular filtration rate is <70 mL/min) and their scores on the cumulative illness rating scale (unfit when the combined score is >6). Treatment regimens are thereafter adjusted accordingly.[83] Fludarabine-based therapies considered standard of care until recently, is unsuitable for use in the older patients with coexisting conditions because it can cause myelosuppression and

infections.[136] Recently, less toxic therapeutic regimens have shown good results in the elderly.

***Concurrent Medications in the treatment of CLL***

Studies have shown that at least 46% of patients on oral cancer therapy are at risk of potential drug-drug interactions (DDI) and 16% have documented harmful DDIs.[137] Another study reported that the frequency of at least one potential DDI occurring in cancer patients was as high as 63%, with 62% of them being major interactions with severe consequences.[138] The prevalence of DDI involving tyrosine kinase inhibitors (TKIs) was found to be over 86% in a cohort of oncology patients, where about 45% were deemed potentially severe.[139] About 93% of CLL patients exposed to treatment have at least one comorbidity and 89% have low to intermediate Charlson comorbidity index score.[140] Pharmacovigilance during CLL therapy is an important consideration in treatment due to the existence of comorbidities in these patients, especially with the newer therapies. The study by Finnes et al reported that concurrent medication metabolized by CYP3A family of enzymes was found in at least 20% of CLL patients commencing treatment with ibrutinib.[141]

Ibrutinib is extensively bio-transformed by CYP3A4, to a large extent, and CYP2D6, to a lesser degree. Other novel agents, CLL oral therapies, idelalisib, acalabrutinib and venetoclax are also similarly extensively metabolized by CYP3A4.[142,143] The CYP3A4 isozyme is responsible for the metabolism of over 50% of all CYP450 metabolized drugs—about 60% of all prescribed drugs are metabolized

through CYP450. This is important because many of the drugs that are taken by older adults are potential enzyme modifiers, causing either inhibition or induction of the CYP450 enzyme. This can affect treatment response, efficacy, and toxicity including QT elongation. The rate of co-prescribing of drugs with potentials to affect TKIs was reported to range from 23%-74%.[144] In addition, proton pump inhibitors have been shown to interact with tyrosine kinase inhibitors when concomitantly administered, affecting the systemic levels of the latter because the chronic acid suppression alters the acidic environment necessary for their absorption.[145] Considering the significant impact of alterations in these enzyme metabolic pathways, and the fact that patients who were routinely on some of these medications were excluded from the clinical trials that established the efficacy of the therapies, it becomes necessary to evaluate the outcome of CLL therapies in the light of their concomitant use with medications for comorbidities and/or adverse effects. Medications for pain, acid reflux, anticoagulants, antiplatelets, antiarrhythmics, CYP3A4 inhibitors, and CYP3A4 inducers can be problematic when administered with CLL therapies.[139,143,146-148]

***Challenges with current CLL Management***

Challenges remain with CLL management as these molecular targets are increasingly integrated into current therapies. Many of the novel agents that have now become standards of care therapies are still under investigation and long-term outcomes and effectiveness are pending, seeing that the first of these agents has only been available for just about seven years. With the emerging protocols that combine novel agents and /or

anti-CD antibodies, better responses for a few years, definite treatment course have been shown, but benefit in OS is still lacking. Treatment for patients with high-risk disease and poor risk factors is still a challenge despite the availability of the novel agents' combo regimens. CLL patients with P53 mutation especially are still inevitably relapsing despite the use of the novel protocols. Richter syndrome transforms the clinical course of CLL disease rapidly into an aggressive lymphoma with poor prognosis. Existing therapies continue to give suboptimal responses and clinical trials outside of intensive CIT remain the only viable option for inducing any appreciable remission.

Clinical trials of new protocols and treatment regimens that are doublets and triplets continue to focus on patients younger than the median age of CLL patients in the US because there is concern about combined toxicities of the targeted agents in older patients. The CLARITY trial is for patients ≤70years of age, while the ECOG and other such large trials for patients older than 70 years have recently provided some insights in sequential/combination treatments with novel agents. [74,88] The issue of sequencing of therapies in order to avoid tumor lysis syndrome (TLS) is fast emerging because some of the novel agents such as venetoclax are able to kill enough cancer cells to induce TLS with its attendant consequences. Sequencing of therapies is needed to mitigate this concern, as is being evaluated in the ECOG trial. One of the current strategies for CLL treatment proposes achieving MRD negativity, which has been associated with deep remissions and possible 'cure". This strategy so far also involves sequencing of therapies starting with treatment induction with CIT, consolidation with novel agents and/ or stem cell transplantation, and maintenance of post induction with immunotherapy.[149]

**STUDY RATIONALE**

The clinical management of CLL has been undergoing considerable transformation of its landscape since the last decade, leading to improved outcomes for patients with the disease. The plethora of treatments that exist have been made more diverse since the last decade. In one study, as many as seventeen different first line therapies in the pre-kinase era were documented.[46] Treatments have moved from monotherapies to combination therapies with monoclonal antibodies, and more recently, to inhibitors of dysregulated pathways and their combinations. Literature reports on the clinical activity and increased use of the novel agents, as well as the toxicity of CT/CIT seem to suggest that the latter has little or no role in today's CLL treatment.[150] Several reports show that ibrutinib because of its improvement on treatment outcomes, toxicity profile and convenient oral formulation presently has taken over as the frontline therapy from regimens such as BR, FCR in many practice settings.[151,109] Despite the wide use of these newer agents as frontline therapies, not all patients can use them. The presence of unique adverse effects, cost and limitless treatment duration may constitute impediments to their effectiveness in real-world use.

Some of the clinical trial results for the novel agents are yet to be duplicated in clinical practice settings. For example, an update from the RESONATE-2 trial, reported ibrutinib discontinuation rate of only 3%;[152] however, real world data demonstrate that ibrutinib discontinuation rates generally range from 26% to 34%, and data from a recent

retrospective study reported an even higher discontinuation rate of 42% among relapsed patients.[104,107,153-155,] Real world data also demonstrate that the median PFS for ibrutinib was 35 months, a value that is much less than the 55 months observed in clinical trials. Furthermore, most clinical trial populations for CLL therapies are comprised of younger participants who can tolerate more aggressive chemotherapies and regimens, consequently yielding results that might not be representative of real-world effectiveness. The paucity of real-world evidence corroborating the effectiveness of these targeted therapies outside of clinical trials means that more research into the real-world outcomes of the treatment with the targeted therapies is needed. Additionally, while the tyrosine kinase inhibitors (TKIs) and the B-cell lymphoma 2 (BCL-2) inhibitors are revolutionizing CLL management, the pharmacoeconomic perspective of these therapies remains a concern. It is therefore pertinent that for CLL therapies, identifying and evaluating what works in the real life through clinical research is critical effort and knowledge that will advance progress towards improving outcomes for sufferers.

The changing treatment landscape, increased use of the novel agents, and the toxicity of CT/CIT seem to suggest that the latter may be of limited use in today's CLL treatment.[156] However, the updated 2019 National Comprehensive Cancer Network Treatment Guideline for CLL recommends that CIT with FCR is still appropriate for the first-line treatment of younger CLL patients with mutated IGHV status because such patients are expected to achieve long PFS, maintenance-free remission and possible 'disease cure'. [73,90,157] Also, more recently, increased number of investigators are reporting reasons why the future may still have a role for anti-CD 20 antibody and CIT,

thus should not be abandoned due to their promising potential in inducing higher MRD negativity when combined in a 'time-limited' treatment course with the targeted therapies.[158,85] What of cases where a patient fails all targeted therapies or presents with a tumor that requires rapid debulking? More recently, studies have suggested a future role for chemoimmunotherapies use as pretreatment to debulk or reduce tumor burden prior to treatment with the targeted therapies. The efficacy of some of such combinations and their comparative analyses with novel therapies are currently being assessed in clinical trials.

Similarly, it is critical to evaluate the outcomes for these frontline conventional therapies in the light of the arrival of the novel therapies, because they may remain clinically relevant in many countries, as these novel agents are yet to be widely available globally. In countries such as the Netherlands, CIT remains the cornerstone of CLL therapy and their treatment guidelines clearly favor its use.[85,159-161]

The rapidly increasing treatment options places a higher demand on clinical experience and evidence in choosing optimal therapy for a person diagnosed with CLL, regardless of the existence of treatment guidelines Recent real-world studies have observed treatment protocols outside of treatment guidelines in different practice settings.[109] It is therefore important to understand treatment patterns, tolerability, and health outcomes and practices for CLL frontline treatments, especially with the advent of therapy with the novel agents. This is with the intention to determine the treatment practices that will aid optimal decisions in choice of effective therapies.

Finally, it is worthwhile to have a baseline upon which the impact of the entrance of the novel agents into CLL management can be tracked, measured and interpreted, to facilitate evaluation and understanding of CLL treatment patterns within the context of the changing treatment paradigms.

What can we learn from records in a large database such as VHA? The proposed study aims to determine real world evidence regarding treatment outcomes in the national VHA population. Coincidentally, the U.S. veteran population offers the best setting that mirrors most CLL risk factors; 46% of veterans are age 65 years and older, 82% are white, 91% are male, and some have been exposed to Agent Orange in the Vietnam War.[161] This makes the VA an ideal setting to study treatments and outcomes for patients with CLL. It will provide real-world evidence regarding CLL therapies in patients with the disease condition in the era of targeted therapy. This will be the largest study to date in this population.

**TRANSLATIONAL APPLICATION**

Translational Science (TS) is the science of focused research that aims to transform knowledge into interventions that improve patient outcomes. Sometimes, this is accomplished by minimizing risk, adverse effects, and costs. Interventions can be in the form of therapeutics, medical devices, diagnostics, processes and procedures, or behavioral changes. Randomized controlled trials (RCTs) remain the gold standard method of determining efficacy for therapeutics in healthcare, but they often do not reflect real world practices and patient outcomes. Real world patients are more diverse

than clinical trials allow, with varied manifestations of comorbidities, polypharmacy, and demographics.

A properly designed study that uses robust clinical data obtained from real-life settings and/or records will yield real world evidence (RWE) that allow for improved interpretation of risks and benefits resulting from long-term use of a drug. This, in turn, can be used for informed decision-making that will improve outcomes. RWE is obtained from analyzing real-world data (RWD). FDA defines RWE as "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD". In other words, RWE is "evidence derived from RWD through the application of research methods". It is not merely passively collected or anecdotal data, but rather results from careful study designs to assess the treatment effects on patient outcomes. Analysis of treatment outcomes may also help in determining the associations that wrap back around to inform and drive basic research. In other words, not only does RWD provide evidence that help translate scientific findings into the everyday care of patients in the general population, but it also helps translate the concerns of the patients, practitioners, and caregivers into scientific inquiry.

Furthermore, observations from basic research may suggest larger clinical studies that may lead to discoveries that change or drive clinical practice. The discovery of CD5- or CD5+ monoclonal B lymphocytes in human peripheral blood in almost 10% of persons over 40 years of age with increasing amounts as age progresses, peaking at about 50% in adults over 90 years, led to the use of monoclonal B cell lymphocytosis as a diagnostic parameter for CLL.[162-65] Also, recent understanding of the biology of CLL led

to the discovery of small molecule inhibitors that target key mechanisms for CLL proliferation and survival with yet to-be- paralleled outcomes in patients, almost irrespective of their underlying genetic anomalies. The entrance of these small molecule inhibitors, the novel agents, into CLL therapy is revolutionizing treatment of patients; however, there is still challenges regarding their use in the real world. Ibrutinib was initially approved by the FDA for the treatment of relapsed CLL without TP53 deletion. However, data from real world use had led to its further approval as first line therapy in high-risk patients and somewhat healthy patients. On the other hand, its real-world use has shown that it is less well tolerated as previously predicted from clinical trials, with moderate to high discontinuation rates. Other knowledge gaps/uncertainties in the therapeutic management of CLL with the newer agents include the challenge of enduring unlimited number of years on the treatment, expense, toxicities, treatment failure arising from lack of adherence, drug resistance and polypharmacy issues such as drug-drug interactions. All of these can potentially limit the use of the newer agents. On the other hand, the chemoimmunotherapies such as FCR, FC, and BR have successfully been used as frontline therapies in CLL patients with different prognostic indices.

Furthermore, the advent of the newer therapies seems to suggest that the use of chemoimmunotherapy may be approaching its end. Will CIT still be useful in CLL patients? For what category of patients? The clinical course of CLL is extremely variable, with many biological features impacting treatment choice, course, and prognosis. It is a disease condition where what works for individual patients differ quite a bit from guideline recommendations and clinical trial results.[113] Analyzing real world outcomes

for CLL therapies based on patient-level data will facilitate appropriate risk-benefit analyses in advancing patient care by selecting therapeutic choices that result in better outcomes.

CLL management is witnessing rapid transformations and transitions, these advances underscore the importance of translational medicine research. It is one of the most active areas in pathogenesis, diagnosis and treatment. CLL is a highly variable disease and research activities in the area research has helped provide the current understanding that combined assessment of clinical, genetic, biological, and physical factors are needed for optimization of therapy, contrary to the days of using only disease presentation. The treatment paradigms in the management of CLL currently lies in the development of therapies that aim to increase efficacy by causing deep remissions that prolong progression free survival and overall survival, reduce toxicities and provide convenient dosing options from both new and existing agents, based on the understanding of the pathology, immunology and disease biology. Such a feat is the hallmark of translational science. Translational research explores the most recent advances in the understanding of the pathogenesis and clinical behavior of the disease and how best to apply these insights to such a rapidly moving target. Studying CLL therapies in a large database, such as the VHA, through properly designed research studies, will potentially advance patient care by identifying the continued roles or otherwise of older CLL therapies, the optimal therapies for best patient outcome and the everchanging treatment landscape. Studies have demonstrated that patients value efficacy in selecting CLL therapies, but they will require essentially large gains in efficacy in order to offset the

disutility associated with risks of prevalence of adverse events as well as cost. Such information can be obtained in real-world clinical settings. Describing recent data on therapeutic regimens and outcomes of treatment for CLL as our study has done, helps to shed more light into understanding how to optimize therapy and current un-met needs, towards optimizing outcome for the patients.

# CHAPTER TWO

# STUDY OBJECTIVES AND HYPOTHESES

## PRIMARY OBJECTIVES

***Aim 1. Describe treatment trends for nine select CLL therapies 2014 to 2018.***

*Hypothesis A1.1*: *Chemotherapy-based therapies will be the most predominantly used CLL treatments for 1L, 2L, and 3L+*

*Hypothesis A1.2: Ibrutinib will be the most common CLL treatment for 1L, 2L and 3L$^{+}$.*

*Hypothesis A1.3: Novel treatments will exceed CT/CIT treatments in 1L, 2L, and 3L+.*

*Hypothesis A1.4: The uptake of CT/CIT will be more in the earlier years of the study; however, novel agents uptake will surpass CT/CIT in the later years of the study.*

*Strategy:* Calculate the proportion of CLL patients using each of the select nine therapies for each line of therapy for each year and determine if there is a difference regarding their use and uptake.

***Aim 2. Determine overall survival (OS) at 6 months for the nine select CLL treatments (1L only).***

*Hypothesis A2.1: 6-month overall survival will be higher with ibrutinib than other therapies.*

*Hypothesis A2.2: Overall survival rate will be higher with novel treatments than with CT/CIT treatments.*

*Strategy:* Calculate the proportion of CLL patients alive at 6 months post treatment initiation for the nine select therapies, CT/CIT, and NA therapies. Determine if there is a difference in OS between the therapies, using ibrutinib as reference and CT/CIT vs NA, using the chi-square test.

***Aim 3. Determine overall survival as a timed outcome, from treatment initiation to death by any cause for the novel agents (NA) and the traditional therapies (CT/CIT), in the first line of therapy.***

*Hypothesis 3: The probabilities of survival will be higher for the novel agents than the CT/CIT in the first line of therapy.*

*Strategy:* Plot a survival analysis curve for patients on CT/CIT and NA therapies, determine and compare average (range) of survival in days using log rank test.

**SECONDARY OBJECTIVES**

***Aim 4. Determine time from diagnosis to treatment initiation (TTFT), time from initiation to discontinuation (TIDC), and time to next treatment (TTNT), for the nine select therapies.***

*Hypothesis 4:* Time to first treatment (TTFT), time from initial treatment to discontinuation (TIDC), and time-to-next treatment (TTNT), will be similar for all 1L therapies.

*Hypothesis A4.2:* Time to first treatment (TTFT), time from initial treatment to discontinuation (TIDC), and time-to-next treatment (TTNT), will be longer for novel agents than with CT/CIT

Calculate the mean ± standard deviation for each timed outcome for the nine select therapies, CT/CIT and NA therapies. Compare and determine if there are any differences using student t-test using ibrutinib as reference group. Compare CT/CIT vs NA.

***Aim 5. Determine and compare health care facility utilization at 6 months (emergency room visits, urgent care visits, hospital admissions) for the nine select therapies.***

*Hypothesis 5:* A higher proportion of patients on CT/CIT will have emergency room visits, urgent care visits, and hospital admissions at 6 months than those on NA therapies.

Determine the specific proportions of patients who utilized each facility-based care at six months for the two groups of therapies. Compare each outcome in the two groups using chi square test. Test of significance is at $P<0.05$.

***Aim6. Determine and compare the pattern of select complications after 6 months of treatment in patients initiated on each of the nine select therapies.***

*Hypothesis A6.1:* There will be no difference in the pattern of select complications between the nine CLL therapies.

*Hypothesis A6.2: All the complications will be more prevalent in the CT/CIT therapies compared to the NA.*

*Hypothesis A6.3: There will be no difference in the proportion of patients with DLBCL between those on FC/FCR/PCR and ibrutinib.*

Strategy: Determine overall complications post treatment initiation, and compare the trend among the nine select therapies, CT/CIT vs NA.

**TERTIARY OBJECTIVES:**

***Aim7. Describe and compare the uptake of 1L CT/CIT and NA therapies for black and white patients.***

*Hypothesis 7:* The black patients will lag behind in the uptake of novel therapies versus the white patients.

Strategy: Determine the uptake of all nine therapies in the 1L for years 2014 -2017, for black and white patient populations. Compare the proportions using chi square test.

***Aim8. Determine if CT/CIT and NA use is different for the age groups <65 years, 65-74 years and >74 years.***

*Hypothesis 8: CT/CIT and NA use will be similar for all age groups.*

Strategy: Create three age-based groups (<65 years, 65-74 years and >74 years) for each of NA and CT/CIT. Determine the proportion of patients on CT/CIT and NA respectively for each age-group.

***Aim9. Determine if FC/FCR/PCR and ibrutinib use and uptake is different for age groups (<65 years, 65-74 years and >74 years).***

*Hypothesis 9:* FCR and ibrutinib use will not be different within each age group.

Strategy: Determine and compare (using chi-square test), the proportion of patients on FC/FCR/PCR and ibrutinib therapies for each age group. Compare the trends on a year by year basis.

***Aim10: Compare use of FCR and ibrutinib for black and white patients in the different age groups.***

*Hypothesis 10: There will be no difference in the use of FCR and ibrutinib for black and white patients in the different age groups.*

Strategy: Determine and compare (using chi-square test), the proportion of black and white patients on FCR and ibrutinib therapies for each age group and compare the differences in the use of both therapies.

***Aim11. Determine if 1L treatment patterns are different for patients with VA priority groups of 1, 2-6, and 7-8.***

*Hypothesis 11.1:* The use of all nine therapies will be similar for patients in all three VA priority groups.

*Hypothesis 11.2: The uptake of CT/CIT and NA therapies will be similar for patients in all three VA priority groups (1, 2-3, 7-8).*

Strategy: Calculate the proportion of patients on the nine select therapies, CT/CIT and NA for each VA priority group using chi-square. Compare differences in uptake between the therapies, using VA group 1 as reference, and CT/CIT vs NA in each group using chi square test.

***Aim 12: Determine the relationship between Charlson Comorbidity Index score and 6 months patient mortality and survival times.***

*Hypothesis 12.1: Charlson Comorbidity Index score will be higher in patients who die than in those who survive.*

*Hypothesis 12.2: Length of survival will be longer for the patients with lower charlson comorbidity index scores for CT/CIT and NA therapies.*

*Hypothesis 12.2: Length of survival will be longer for the patients with lower charlson comorbidity index scores for CT/CIT and NA therapies.*

Strategy: Compare the average Charlson Comorbidity index score for patients who die and those who survive within six months of treatment initiation.
Classify patients in each treatment group into one of three CCI categories, stratified in accordance with Charlson age score, CCI 1-3 (Low severity), CCI 4-7 (Moderate - High severity) and CCI ≥ 8 (High severity). Compare the association between CCI scores and survival times in each therapy (CT/CIT and NA) and for NA vs CT/CIT, using the low CCI category as reference with student t-test.

***Aim 13: Determine the relationship between co-medications and patient mortality at 6 months post treatment initiation.***

*Hypothesis 13.1: The proportion of patients on select co-medications that are dead at 6 months will be same all nine therapies.*

*Hypothesis 13.2: The proportion of patients on select co-medications that are dead or alive at 6 months will be same for CT/CIT and NA therapies.*

*Hypothesis 13.3: Being on each of the select co-medications will increase the risk of death for patients in the CT/CIT, NA, FC/FCR/PCR and Ibrutinib therapies.*

*Strategy:* Compare the percentage of patients on co-medication(s) who died and those who survived within six months of treatment initiation for nine select therapies, CT/CIT and NA. Determine the relative risk of death for each of the concomitant medications for each therapy and for CT/CIT and NA.

# CHAPTER THREE

# STUDY APPROACH AND METHODOLOGY

## STUDY METHODS

### *Study Design*

This study is a retrospective cohort study of adult patients (at least 18 years old) with CLL in the VHA from 2014-2018. Historical data wase examined for up to 20 years prior to the study period.

*Data Source*

The VHA, with healthcare facilities in all 50 states, is the largest integrated health care system in the United States. It maintains an electronic medical record system, which includes administrative, clinical, laboratory, and pharmacy data repositories. These repositories include data from both hospital and clinic settings, providing visit-level information (VA MedSAS patient care datasets), patient-level (VA Master Vital Status and VA Mini Vital Status datasets), and VA Pharmacy Benefits Management Inpatient and Outpatient datasets. These data sets are linked together at patient level, using a unique patient identifier, making it possible for information for individual patients to be obtained across the datasets. Furthermore, the VHA system maintains a vital status file that enables investigators to determine patient mortality, even when it occurs outside the clinic or hospital. The study utilized these internal VHA databases for the study.

Variables relevant to providing information for our study questions were created and used to build an analytic dataset for the study. Some of the variables of interest for

example, patients' demographics, were already existing as such in the electronic data system.

### *Study Population*

The study population consist of adult patients (at least 18 years old) with CLL diagnosis from VHA facilities across the United States. The sub-population with exposure to treatment with frontline therapies or novel agents for CLL between 2014-2018 were further analyzed for different therapies and outcomes.

#### *Eligibility Criteria*

CLL patients (adults ≥18 years at date of CLL diagnosis) on treatment with a frontline agent (or their combinations) or novel agent for CLL in the patient identification period (index period) are assessed. *ICD9* code 204.1x and *ICD10* code 91.1x were used for the identification of patients. Patient selection based on the number of office visits and availability of EMR was used as criteria to establish accessing care from VA.

#### *Sample Size*

Preliminary counts of patients with CLL diagnosis within the study period in the VHA system yielded numbers greater than 26,000 CLL patients. The number of CLL patients on the select drug therapies will be determined as part of the study through actual counts in the database. Preliminary estimates suggest that approximately 4,000 patients will have received these therapies. This is a descriptive, population-based study, so the study sample comprises all patients in VHA system that meet the inclusion criteria—not just a subset of the population.

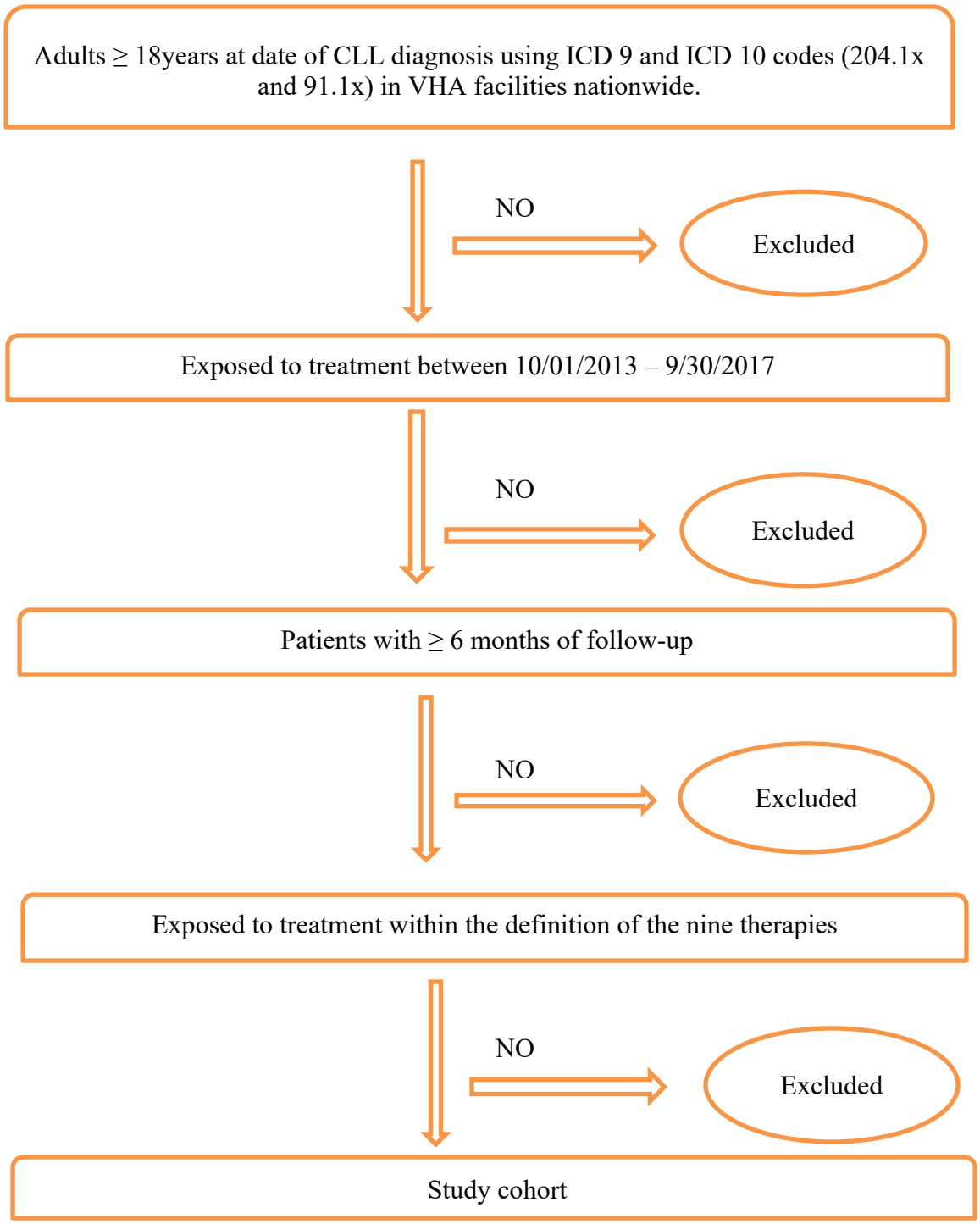



**Figure 3.1** Attrition Diagram: Overview of Cohort determination

***Data Collection Approach***

Patient identification period (pre-index period) is from 2014-2018. Index date is defined as date of initiation of CLL related novel treatment (order date for oral medications or treatment administration date for IV regimens). The follow-up period allows patients to be followed for a minimum of 6 months post-index. Patients will be followed until the last VA visit, loss to follow-up, a record of death, or end of the study period, whichever occurs earlier. SAS association rules and coding algorithms were used to create variables that represent the nine select therapies groupings.

*Study Time Period*

*Study period*: 2014- 2018 (including 6 months of follow up)

*Patient identification period (index period)*: Oct 1, 2013-Sept 30, 2017

*Index date*: date of initiation of CLL related systemic treatment (order date for oral medications or treatment administration date for IV regimens)

*Pre-index period (baseline/observation period)*: all data available before index date since 10/01/1993

*Follow-up period*: allows patients to be followed for a minimum of 6 months post-index. Patients were followed until last VA visit, loss to follow-up, record of death, or end of study period, whichever occurred earlier.

***Exposures and Treatment Patterns:***

The study drugs selected from FDA approved drugs for the treatment of CLL are listed in table 3.1. CLL patients with a frontline agent and/or novel agent for CLL in the

patient identification period (index period) were assessed. Although CLL treatment is one of the fastest changing oncology treatment landscape, we have included the most innovative and clinically relevant treatment options for CLL pharmacotherapy as at the time of the study development. The drugs were assessed from the database using three identifiers, generic name, National drug code (NDC) and current procedural terminology / Healthcare common procedure coding system (CPT/HCPCS).[166,167]

| **Drug Class** | **Drug name (Generic)** | **Drug Name (Brand)** |
|---|---|---|
| Nucleoside analogues (chemotherapy based) | Fludarabine Phosphate | Fludara, Oforta |
| | Pentostatin | Pentostatin, Nipent |
| Alkylating agent (chemotherapy based) | Cyclophosphamide | Cytoxan, Cytoxan Lyopholized, Neosar |
| | Chlorambucil | Leukeran |
| | Bendamustine Hydrochloride, Bendamustine, | Balrapzo, Bendeka, Treanda |
| Anti-CD20 monoclonal antibodies (immunotherapy based) | Rituximab, Rituximab Hyaluronidase, Rituximab-Abbs, | Rituxan, Rituxan Hyclea, Truxima |
| | Obinutuzumab | Gazyva |
| | Ofatumumab | Arzerra |
| | Alemtuzumab | Campath, Lemtrada |
| Bruton Kinase inhibitor (Targeted therapy) | Ibrutinib | Imbruvica |
| Phosphatidylinositol 3-kinase inhibitor (Targeted therapy) | Idelalisib | Zydelig |
| | Duvelisib | Copiktra |
| Bcl-2 inhibitor (targeted therapy | Venetoclax | Venclexta |
| Immunomodulatory | Lenalidomide | Revlimid |

**Table 3.1:** Study Drugs

*Study Therapies*

For the purpose of the study, clinically relevant CLL monotherapies, chemotherapies, chemoimmunotherapies (chemotherapy + anti CD20 monoclonal antibody), and novel therapies were identified in accordance with NCCN treatment guidelines and clinical judgement.[90] They were further categorized into nine select therapy groups, as defined in table 2. Outcomes and treatment patterns were evaluated based on these select therapies and three lines of therapy, first line (1L), second line (2L), third line or greater ($3^{+}$L), designated according to the different treatments a patient received.

| **Treatment** | **Root (OR)** | **Combination (AND)** | **Exclude (NOT)** |
|---|---|---|---|
| BR | bendamustine | rituximab | fludarabine, cyclophosphamide, pentostatin, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, OTHER [alemtuzumab, lenalidomide], chlorambucil, CD20 subset [ofatumumab, obinutuzumab] |
| FR/FCR/PCR (+/- CD20) | fludrabine, cyclophosphamide, pentostatin | rituximab | bendamustine, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, OTHER [alemtuzumab, lenalidomide], chlorambucil |
| Ibrutinib (+/- CD20) | ibrutinib | | bendamustine, fludrabine, cyclophosphamide, pentostatin, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, OTHER [alemtuzumab, lenalidomide], chlorambucil |

**Table 3.2.** Definition of Nine Select therapies.

| Treatment | Root (OR) | Combination (AND) | Exclude (NOT) |
|---|---|---|---|
| PK13 inhibitor (+/- CD20) | idelalisib, duvelisib, copanlisib, alpelisib | | bendamustine, fludrabine, cyclophosphamide, pentostatin, ibrutinib, venetoclax, OTHER [alemtuzumab, lenalidomide], chlorambucil |
| Venetoclax (+/- CD20) | venetoclax | | bendamustine, fludrabine, cyclophosphamide, pentostatin, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], OTHER [alemtuzumab, lenalidomide], chlorambucil |
| Chlorambucil (- CD20) | chlorambucil | | bendamustine, fludrabine, cyclophosphamide, pentostatin, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, OTHER [alemtuzumab, lenalidomide], CD20 [rituximab, ofatumumab, obinutuzumab] |
| CD20 + Chlorambucil | CD20 [rituximab, ofatumumab, obinutuzumab] | chlorambucil | bendamustine, fludrabine, cyclophosphamide, pentostatin, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, OTHER [alemtuzumab, lenalidomide] |
| CD20 mono | CD20 [rituximab, ofatumumab, obinutuzumab] | | bendamustine, fludrabine, cyclophosphamide, pentostatin, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, OTHER [alemtuzumab, lenalidomide], CD20 [rituximab, ofatumumab, obinutuzumab], chlorambucil |
| Other | alemtuzumab, lenalidomide | | bendamustine, fludrabine, cyclophosphamide, pentostatin, ibrutinib, PK13 [idelalisib, duvelisib, copanlisib, alpelisib], venetoclax, CD20 [rituximab, ofatumumab, obinutuzumab], chlorambucil |

**Table 3.2(CONTD)** Definition of Nine Select therapies.

***Definitions:***
**Combination**=all combination and exclude criteria must be met within 60 days of the root drug to call the regimen a combination.
**Start date**=first date for any of the root drugs, but all combination and exclude criteria must be met within 60 days of that date to ensure the person is on the combination therapy.
**Stop date**=last date for any of the root drugs, but all combination and exclude criteria must be met within 60 days of that date to ensure the person is still on combination therapy.
**6MGap**=if the patient does not receive the same treatment for more than 6 months, then use the stop date that occurred before those 6 months and call anything thereafter a new line of therapy (LOT).
**Lines of Therapy:**
**1L**= first treatment the patient received.
**2L** = second treatment the patient received.
**3LP = (3L+)** = third or greater treatment the patient received.

**Table 3.3.** Eligibility Criteria for the Nine Select Therapies and Lines of Therapy.

***Description and measurement of study variables***

The study assessed several independent variables which were used in our analyses. They include the following:

*Baseline patient demographics*

All demographic characteristics were documented at baseline including variables captured within 12 months prior to the index date.

- Date of death
    - Age at index date (#) Calculated as: integer [ (index date – date of birth + 1) / 365.25]
    - Age groups (<66, 65-75, 75+)

- Patient sex (y/n)
    - Male, female
- Patient race (y/n)
    - White, Black/African American, Other.
- VHA priority group (#) 1, 2-6, 7-8
- Geographic region (VSN 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 16, 17, 19, 20, 21, 22, 23)
- Prior history of Agent Orange exposure (y/n)

**VA PRIORITY GROUPS**

VA priority group is a grading system that assigns a number (1 to 8) to veterans enrolled in the VA healthcare program, for the purpose of accessing healthcare. The assignation of group is primary based on military service history, disability rating, income level, medicaid eligibility, and other benefits received from, such as VA pension benefits). Highest priority is assigned to those with service-driven disability and the lowest is assigned to those with higher income and do not have service-connected disability. They utilize this priority grouping to balance healthcare demand with VA healthcare resources.[168] Since this is a resource sharing structure, it may influence types of medications accessed as well as affordability by the different groups. Some features of the priority groups are described in table 3.4.

| VA Priority Group | Definition | Benefit |
|---|---|---|
| **1** | Veterans with service-connected, rated as 50% or more disabling, or renders one unemployable, or received the Medal of Honor (MOH) | N pay copays for any types of care, tests, or medications. |
| **2** | Veterans with service-connected, rated as 30% - 40% disabling | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services unrelated to military service<br>No co-pay for first 3 urgent care visits and $30 subsequently. |
| **3** | Veterans who are former prisoners of war (POW), or Received the Purple Heart medal, or discharged due to disability that was caused by—or got worse because of—active-duty service, or have a service-connected disability rated as 10% or 20% disabling, or fall into the special eligibility class due to being disabled by treatment or vocational rehabilitation. | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services unrelated to military service<br>No co-pay for first 3 urgent care visits and $30 subsequently. |
| **4** | Veterans receiving VA aid and attendance or housebound benefits or have received a VA determination of being catastrophically disabled. | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services unrelated to military service<br>No co-pay for first 3 urgent care visits and $30 subsequently. |

**Table 3.4.** Select characteristics of VA Priority Groups (Adapted from https://www.va.gov/health-care/eligibility/priority-groups/

| VA Priority Group | Definition | Benefit |
|---|---|---|
| **5** | Veterans that don't have a service-connected disability, or you have a non-compensable service-connected disability rated as 0% disabling and have an annual income level that's below VA's adjusted income limits (based residential zip code). Those receiving VA pension benefits or are eligible for Medicaid programs, are assigned to this group. | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services unrelated to military service<br>Pays co-pay for outpatient services unrelated to military service<br>No co-pay for first 3 urgent care visits and $30 subsequently. |
| **6** | Veterans who served in Vietnam between 1962 – 1975, those discharged less than 5 years ago, exposed to ionizing radiation during the occupation of Hiroshima and Nagasaki, served in the Persian Gulf war between 1990-1998, served in camp Lejeune for at least 30 days between 1953 – 1987 or served in a theater of combat operations after November 11, 1998 are assigned to this group | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services unrelated to military service<br>$0 or $30 co-pay for first 3 urgent care visits (depending on if condition is covered by special authority like agent orange) and $30 subsequently. |
| **7** | Veterans whose gross household income is below the geographically adjusted income limits (GMT) for where you live, and who agree to pay copay. | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services<br>Pays full co-pay or reduced co-pay for in-patient care, if residing in high cost area.<br>$30 co-pay for urgent care visits. |
| **8** | Veterans whose gross household income is above VA income limits and geographically adjusted income limits for where you live, and who agree to pay copays. | Pays a co-pay of $8 -$9 for medications.<br>Pays co-pay for outpatient services<br>Pays full co-pay or reduced co-pay for in-patient care, if residing in high cost area.<br>$30 co-pay for urgent care visits. |

**Table 3.4(CONTD)** Select characteristics of VA Priority Groups (Adapted from https://www.va.gov/health-care/eligibility/priority-groups/

***VA Geographic Region***

The VA is structured into regional areas called Veterans Integrated Service Networks (VSN #), with numbers assigned to each regional area. Each geographical region oversees the operations of a number of health centers, nursing homes, outpatient clinics, VA hospitals, and other VA healthcare facilities. Geographic variations in healthcare utilization, resource allocation and access to care has been reported for the VA VISNs. The number of patients, average annual cost per person and resource utilization were shown to significantly vary across VISNs.[169]

***Specific treatment characteristics***

Specific treatment characteristics are as follows:

- *Start date* is the first treatment administration date of the first dose of monotherapy.
- *End date* is the last treatment administration date of the last dose of monotherapy. If the patient is lost to follow-up, then the last recorded VA visit date will be utilized.

- *Line of Therapy (LOT)*

Treatment uptake and trends were assessed on three lines of therapy namely, first line (1L), second line (2L), third line and above (3L+), based on the different treatments a patient received, their timing and duration. Treatment regimen was

considered first-line, if index date falls within time between initial diagnosis and first drug claim. Thereafter, a new line of therapy occurs when a patient does not receive the same treatment for more than 6 months. The stop date for that regimen was considered as the last date that it occurred before those 6 months, and anything thereafter was regarded as new line of treatment (LOT).

***Concomitant medications*** (medications being taken at the time of treatment initiation)

The electronic health record (HER) of the eligible patients was assessed, and the use of any of the medications below, prior to the index period was recorded for the affected patients.

- Anti-hypertensives
- Anticoagulants
- CYP3A4 inhibitors
- CYP3A4 inducers
- Gastric acid-suppressing drugs
- Antiarrhythmics
- Drugs used for pain

***Comorbidities***

We assessed Charlson comorbidities and other comorbidities as defined by ICD-9-CM and ICD 10 codes.

- Charlson comorbidities (y/n) and score (#, calculated) (using data in 24 months prior to index date)
    - Fiscal years 1994-2015 (ICD-9-CM) were used.[170]
    - Fiscal years 2016-2017 (ICD-10) were used.[134]
- Prior history of additional comorbidities (y/n) (using data in 24 months prior to index date)
    - Coronary artery disease, atrial fibrillation, arrhythmia, deep vein thrombosis, pulmonary embolism, prior bleed, lung diseases, intestinal disorders (Crohn's disease and GI ulcers), high uric acid or gout, high cholesterol, hypertension, and rheumatoid arthritis.

*Defining Charlson Comorbidity Index (CCI) Scoring System*

Charlson comorbidity score predicts 10-year survival for patients with multiple comorbid health conditions. Each comorbidity attracts a score of 1, 2, 3, or 6, based on the associated risk of dying due to that condition. Core morbidities and how to calculate the CCI points based on assign scores are shown in Table 3.5.

| CONDITION | SCORING | |
|---|---|---|
| **Age** | <50years | 0 |
| | 50 – 59 years | +1 |
| | 60 – 69 years | +2 |
| | 70 – 79 years | +3 |
| | ≥80 years | +4 |
| | | |
| **Myocardial Infarction** History of definite or probable MI, (EKG and/or enzyme changes). | Yes | +1 |
| | No | 0 |
| | | |
| **Congestive Heart Failure** (external or aproxysmal dyspnea and has responded to digitalis, diuretics or other afterload reducing agents). | Yes | +1 |
| | No | 0 |
| | | |
| **Peripheral vascular disease**. Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm) | Yes | +1 |
| | No | 0 |
| | | |
| **CVA** or **TIA** (History of a cerebrovascular accident with minor or no residual and transient ischemic attacks) | Yes | 0 |
| | No | +1 |
| | | |
| **Dementia** Chronic cognitive deficit | Yes | +1 |
| | No | 0 |
| | | |
| **COPD** | Yes | +1 |
| | No | 0 |
| | | |
| **Connective Tissue Disease** | Yes | +1 |
| | No | 0 |

**Table 3.5:** ***Charlson Comorbidity Index (CCI) Scoring System***

| CONDITION | SCORING | CONDITION |
|---|---|---|
| **Peptic ulcer disease**<br>Any history of treatment for ulcer disease or history of ulcer bleeding | Yes | +1 |
| | No | 0 |
| | | |
| **Liver disease**<br>Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension) | None | 0 |
| | Mild | +1 |
| | Moderate to severe | +3 |
| | | |
| **Diabetes mellitus** | None or diet-controlled | 0 |
| | Uncomplicated | +1 |
| | End organ damage | +3 |
| **Hemiplegia** | Yes | +2 |
| | No | 0 |
| | | |
| **Moderate to severe CKD**<br>Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L) | Yes | +2 |
| | No | 0 |
| | | |
| **Solid Tumor** | None | 0 |
| | Localized | +2 |
| | Metastatic | +6 |
| | | |
| **Leukemia** (acute or chronic) | Yes | +2 |
| | No | 0 |
| | | |
| **Lymphoma** | Yes | +2 |
| | No | 0 |
| | | |
| **AIDS** (not just HIV positive) | Yes | +6 |
| | No | 0 |

**Table 3.5 (CONTD):** ***Charlson Comorbidity Index (CCI) Scoring System***

***Laboratory values***

Select lab values of interest were captured at multiple time points during the entire study period to allow for potential longitudinal analyses when necessary. The absolute value and dates for all lab values were obtained from EMR where available in addition to capturing categories (e.g. elevated, normal, low) in EMR as available.

- White blood cell count
- Platelets

- Serum creatinine
- Creatinine clearance was calculated using the following formula:

CrCl= [[140 - age(yr)]*weight(kg)]/[72*serum Cr(mg/dL)]

(multiply by 0.85 for women)

**Outcomes**

The primary outcome is overall survival (OS) rate for the different select therapies that are the focus of the study. Additional outcomes include length of survival (OS) from treatment initiation until death from any cause (without time limit), time-to-first treatment (TTFT), time to initial treatment discontinuation (TIDC), time-to-next treatment (TTNT), complications 6 months post therapy initiation including secondary malignancies, emergency room visits, urgent care visits, and hospital admissions. These outcome variables were assessed for the study period.

*Outcome variables:*

- Number of emergency room visits at 6 months post index date (#).
- Number of urgent care visits at 6 months post index date.
- Number of hospital admissions 6 months post index date (#).
- Death in 6 months post index date (y/n)
- Days of survival within 6 months index date (#, calculated)
- Days of survival after CLL agent start date (#, calculated)
- Days between CLL diagnosis and first drug treatment or pharmacy order fill. (#, calculated)
- Survival analysis was conducted as overall survival (OS) from treatment initiation to death and from treatment initiation time to death by any cause.
- Time to Next Treatment was computed as the time from the initiation of the first treatment of CLL agent until the start of a new treatment or addition of drug to current treatment regimen.
- Treatment complications (health conditions that develop in 6 months after treatment start date).
- Health conditions that develop in 6 months after treatment start (y/n, date).
    - Diffuse large B-cell lymphoma (ICD9 & ICD10) (200.6 & C83.3)
    - Hodgkin's lymphoma (201 & C81)
    - allogeneic hematopoietic stem cell transplant (V42.82 & Z94.84)
    - Secondary malignancy (skin cancer, lung cancer, prostate cancer)

*Calculation of some outcome variables*:

- ***Survival Analysis:*** Two approaches were used in measuring survival at the end of study period. Patients who did not die were censored on the last visit date available in the database or at study end date, whichever occurred first.
  - *Approach 1: Overall Survival (*OS) at 6 months post index date. OS was defined as the interval from the initiation of treatment until date of death from any cause within 6 months of treatment initiation.

    OS = [ $Death\ date$ (within 6 months of index date) − $index\ date$ + 1]/30.44

  - *Approach 2*: Overall Survival (OS) from treatment initiation to death was defined as the interval from the initiation of CLL treatment until date of death from any cause (no time limit).

    OS = [ $Death\ date$ (no time limit) − index $date$ + 1]/30.44

***Time to First Treatment (TTFT)***

Computed as time from initial diagnosis until treatment initiation.

- TTFT = [First CLL treatment date - Diagnosis date + 1]/7.0246

***Time to Next Therapy (TTNT)***

Computed as the time from the end of the first treatment until the start of new treatment. Patients who did not move on to next therapy or were still on therapy at the end of study were censored at the study end date or the last visit date available in the database.

- TTNT = [Start of next therapy - first treatment end date + 1]/ 30.44

***Time to Treatment Discontinuation (TIDC)***

Computed as time from initial treatment until change/end in first treatment without treatment completion.

- TIDC = [1$^{st}$ date of incomplete / discontinuation of first therapy - first CLL treatment date + 1]/ 30.44

**Statistical Analysis Plan and Results**

Statistical analyses were performed using JMP and SAS (SAS Institute, Inc., Cary, NC) statistical software. Patients were grouped according to which of the nine select therapies they received, also according to what treatment they received as first line, second line and third line+ as appropriate. Results are reported in aggregate. The number and percent of patients along with descriptive statistics (mean, standard deviation, median, and interquartile ranges, number of non-missing and number of missing values) are reported for continuous data.

Dichotomous variables are reported as counts and percentages. Categorical variables (e.g., age groups, lab value groups, etc.) – sometimes created from continuous variables –have the number and percent of patients reported. In case of missing observations, the number and percentage of missing are reported. Demographic and clinical characteristics are compared among the different strata by using Chi-square/Fisher's exact test (for dichotomous or categorical variables), and student's *t*-test (for the continuous variables). Statistical significance is determined by $P < 0.05$. Time-to-event outcomes were estimated by Kaplan-Meier. Log rank tests were used to compare survival times between groups of different treatments/agents/regimens**.**

## Ethical Considerations

This research work does not contain any studies with human or animal subjects performed by any of the authors.

### *Protection of Human Subjects*

The investigators will perform the observational study in accordance with the regulations and guidelines governing medical practice and ethics in the United States and in accordance with currently acceptable techniques and expertise. The final protocol of the observational study and its amendments were approved in writing by the Institutional Review Boards (IRBs) at the University of Texas Health San Antonio and South Texas Veterans Health Care System.

***Subject Informed Consent***

Not applicable. This is a retrospective observational study. The study investigators received IRB waiver for the informal consent requirement.

***Confidentiality of Study/Subject Data***

The research involves existing data only. No patients or providers were contacted. The data will be maintained in limited-access directories on VA research servers behind the VA firewall at all times. Personnel with access to the data are fully trained and monitored regarding knowledge and practice of good data security processes. Additionally, all data collection will be performed at the South Texas Veterans Health Care System (STVHCS), Audie L. Murphy VA Hospital, San Antonio, Texas, by researchers with VHA appointments. Only these researchers will have access to patient identifiers to enable them merge databases. All electronic data will be stored on a VA research server; therefore, a data security breach is unlikely. Data will be reported only in aggregate, for groups of patients, never at an individual level.

# CHAPTER FOUR
# RESULTS

**Aim 1: Describe trends for nine select CLL treatments from 2014 to 2018.**

***Hypothesis A1.1: CLL treatments will be used equally in all lines of therapy.***

**Strategy A1.1:** Determine the proportion of patients receiving each select treatment in each line of therapy (i.e., treatment count for a given line divided by treatment count across all lines). Compare the proportions to determine if each CLL treatment was used equally in all lines of therapy.

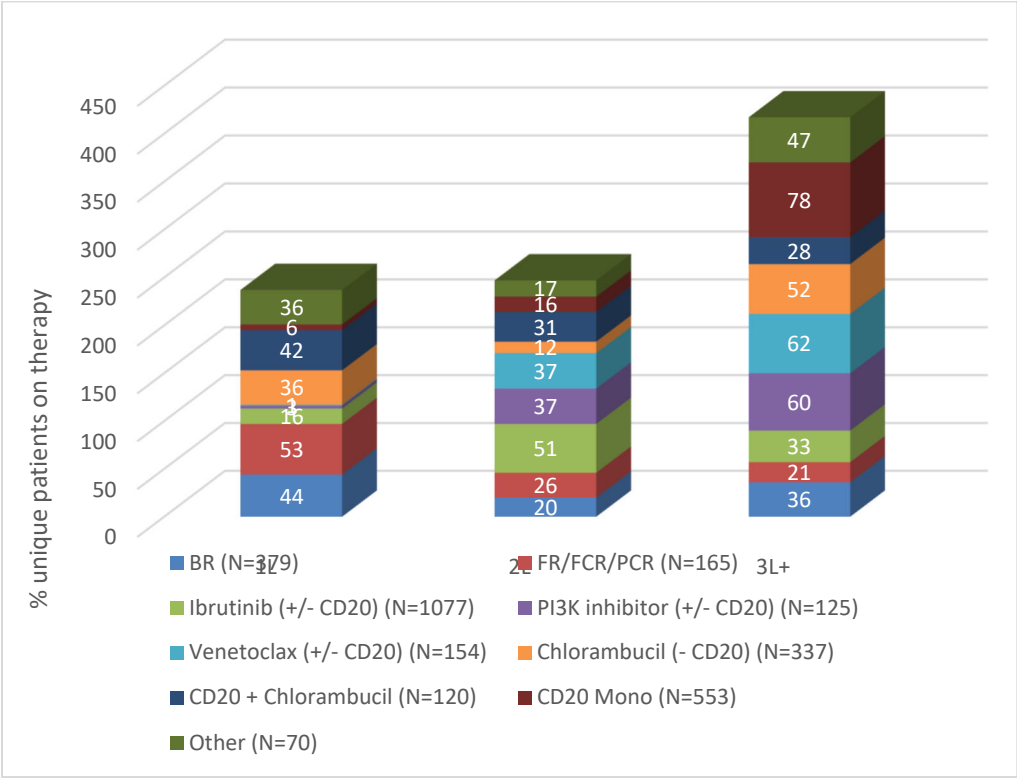



**Figure 4.1.** Proportion of each CLL treatment in each line of therapy **(A1.1)**

**Interpretation A1.1:** FR/FCR/PCR (53%), BR (44%), and Chlorambucil+CD20 (42%) were used more frequently in 1L than the other lines. Ibrutinib (51%) was used more frequently in 2L than the other lines. Finally, CD20 monotherapy (78%), venetoclax (62%), PI3K inhibitors (60%), and Chlorambucil-CD20 (52%) were used more frequently in 3L+ than the other lines.

**Conclusion A1.1**: Reject the hypothesis as there were clear differences in the proportions of CLL treatments used in the different lines of therapy.

***Hypothesis A1.2: Ibrutinib will be the most common CLL treatment for 1L, 2L, and 3L+.***

**Strategy A1.2:** Determine the proportion of patients in each line that received each CLL treatment (i.e., count for one CLL treatment in a given line divided by count for all CLL treatments in a given line). Compare the proportions within a given line to determine which CLL treatments were used most frequently for that line.

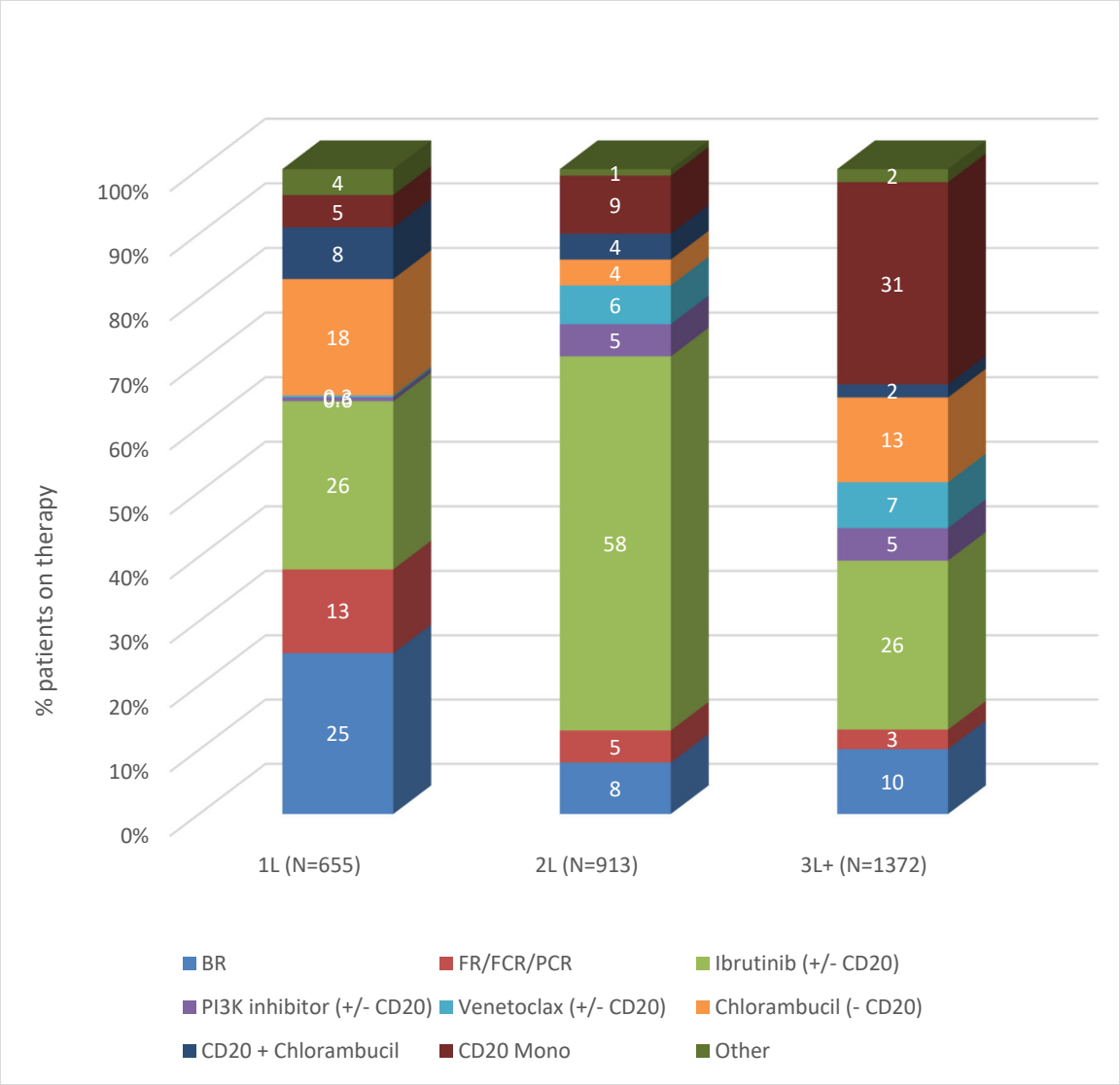



**Figure 4.2.** Proportion of patients on each CLL treatment in each line of therapy **(A1.2)**

**<u>Interpretation A1.2</u>:** For 1L, ibrutinib (26%) and BR (25%) were the most common CLL treatments. For 2L, ibrutinib (60%) was the most common CLL treatment. For 3L+, CD20 monotherapy (31%) and ibrutinib (26%) were the most common CLL treatments.

**Conclusion A1.2:** Accept the hypothesis for 1L and 2L, as ibrutinib was the most common CLL treatment in those lines but reject the hypothesis for 3L+ as ibrutinib was the second most common CLL treatment for that line.

***Hypothesis A1.3: Novel Agents (NA) will be used more often than Chemotherapy /Chemoimmunotherapy (CT/CIT) treatments in 1L, 2L, and 3L+.***

**Strategy A1.3:** Create NA treatment group by combining patients on ibrutinib, venetoclax, and PI3K. Create a CT/CIT group by combining patients on the rest of the treatments. Then, determine and compare the proportion of patients on NA and CT/CIT for each line of therapy.

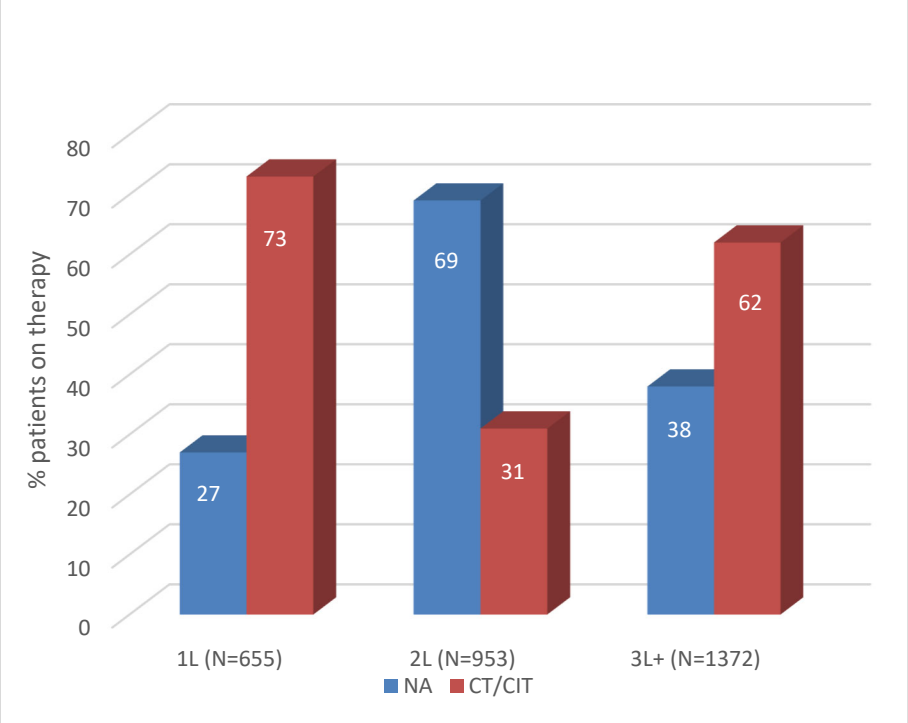



**Figure 4.3** Distribution of novel agents and CT/CIT within the lines of therapy **(A1.3.)**

**Interpretation A1.3:** CT/CIT was used more often than NA in 1L (73% vs. 27%) and 3L+ (62% vs. 38%). NA were used more often than CT/CIT in 2L (69% vs. 31%).

**Conclusion A1.3:** CT/CIT treatments were more common for 1L and $3^{+}$L lines of therapy, while the novel agents were the predominant treatments in the 2L. Accept the hypothesis for 2L but reject it for 1L and 3L.

***Hypothesis A1.4: NA will surpass CT/CIT as the most common CLL treatment in the later years of the study.***

**Strategy A1.4:** Determine and plot the proportion of patients on NA and CT/CIT by line and by year.

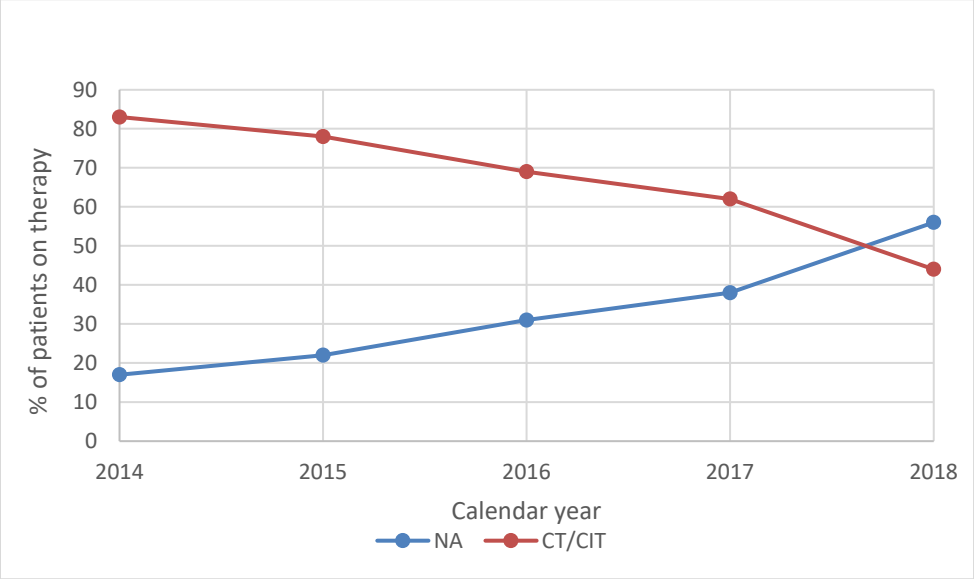



**Figure 4.4** Proportion of patients on NA and CT/CIT, as 1L, by year (2014-2018) (**A1.4.1.**)

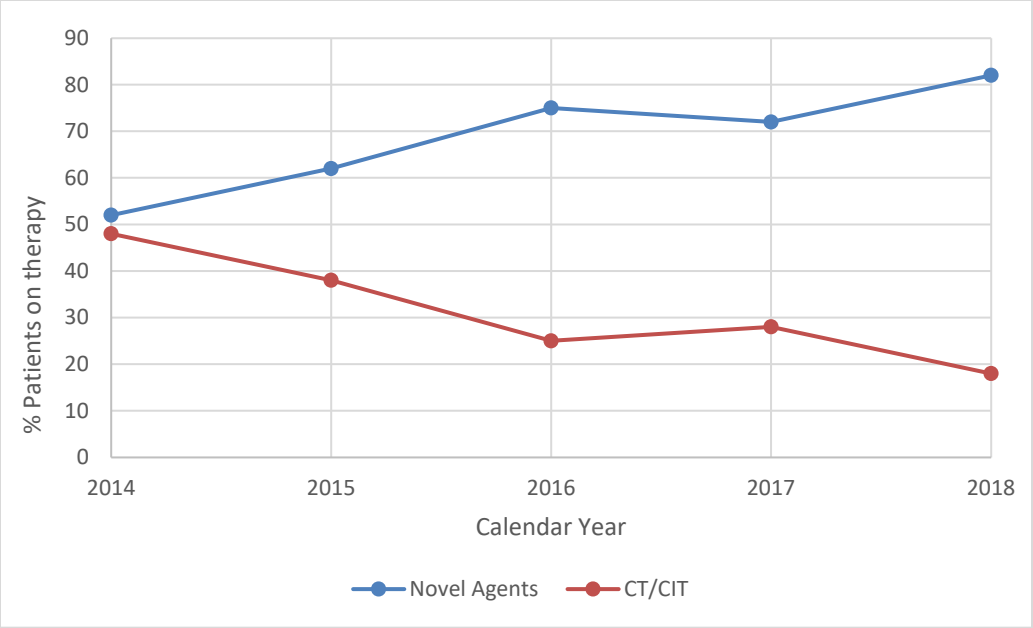



**Figure 4.5** Proportion of patients on NA and CT/CIT, as 2L, by year (2014-2018) **(A1.4.2)**

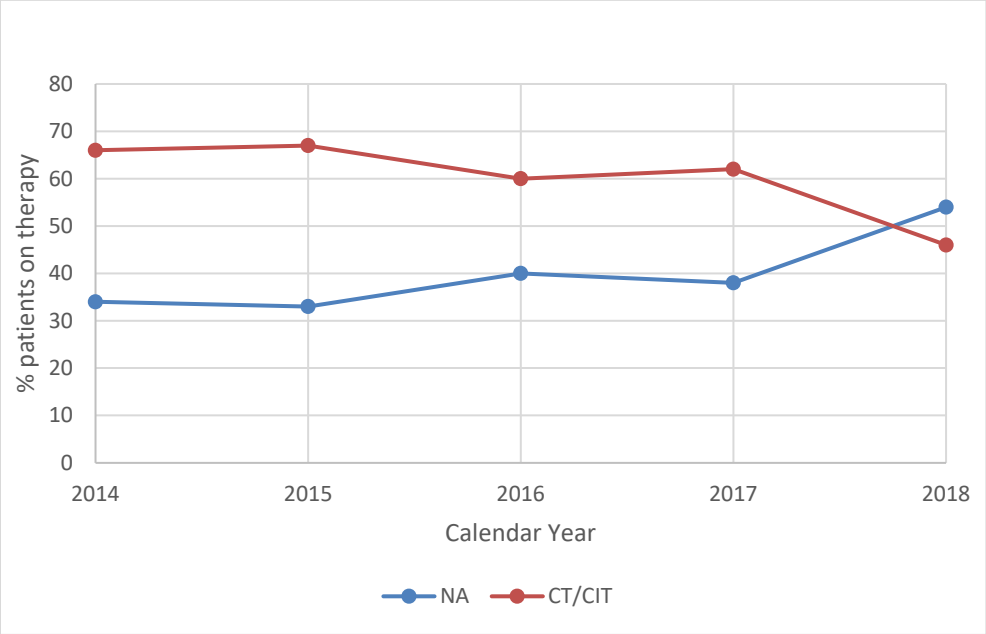



**Figure 4.6** Proportion of patients on NA and CT/CIT, as 3L+, by year (2014-2018) **(A1.4.3)**

**Interpretation A1.4:** For 1L, there was a gradual decline in the use of CT/CIT with a corresponding gradual increase in the use of NA. Eventually, in 2018, NA use was more common than CT/CIT use. For 2L, NA were more common than CT/CIT at the beginning of the study period. NA use increased and CT/CIT decreased throughout the study. For 3L+, there was a gradual decline in the use of CT/CIT, with a corresponding gradual increase in the use of NA. Eventually, in 2018, NA use was more common than CT/CIT use.

**Conclusion A1.4:** Accept the hypothesis, as NA use surpassed CT/CIT use for all lines of therapy by the end of the study period.

## STUDY POPULATION FOR REMAINING AIMS:

The overall study included a total of 1456 patients, 99% males and 1% females who met the study criteria. Of this number, 655 (45%) patients received one of nine select treatments of interest as first line (1L) CLL treatment, and these are the focus of the remaining aims. From this point forward, all analyses are limited to only those 655 patients.

### Baseline Patient Characteristics

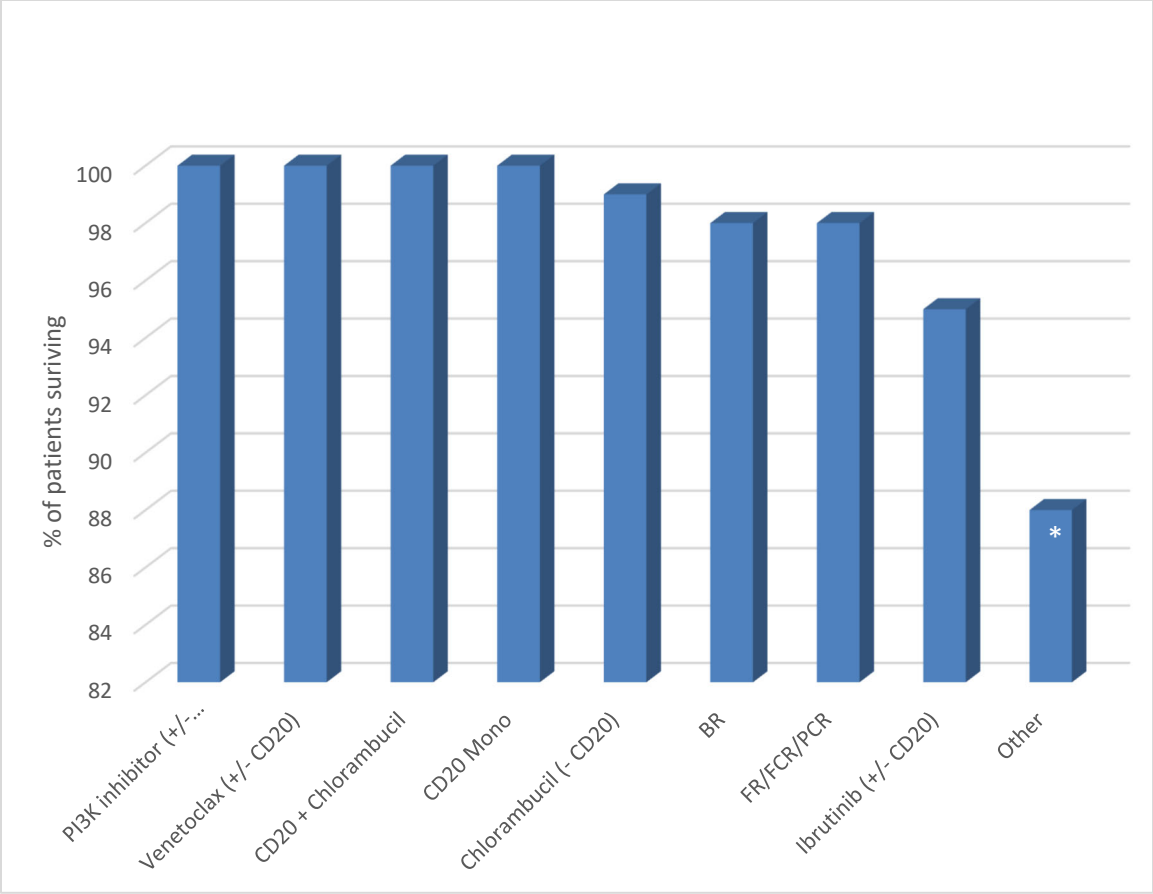
Patients on this first line of therapy had a median age of 70 years (interquartile range 33-90 years), and were predominantly of white race (85%), black race (14%), and other races (1%). Most of the patients were between ages 65-74 years (47%), followed by patients <65 years (24%), and those > 74 years (29%). Major Charlson comorbidities observed at baseline were diabetes (with and without complications (43%), COPD (22%),

renal disease (13%), and congestive heart failure (10%). The average Charlson age score was 5 (range 1-10). Additional clinical conditions occurring at ten percent and above, observed at baseline include hypertension (24%), coronary heart disease (13%), arrhythmia (13%) and atrial fibrillation (11%). 9% of the population had agent orange exposure.

**Aim 2: Determine and compare Overall Survival (OS) at six months for nine select CLL treatments.**

***Hypothesis A2.1: OS at six months will be higher with ibrutinib than other therapies.***

**Strategy A2.1:** Limit the study population to only those patients who had at least 6 months of follow-up. Determine OS at six months for patients on each of the nine select treatments. Using the ibrutinib survival rate as the reference group, compare the survival rate for each of the other eight treatments using the chi-square statistic. Call p-values less than 0.05 statistically significant.




*P<0.05, with reference to ibrutinib.

**Figure 4.7** OS at 6 months for nine select CLL treatments **(A2.1.)**

**Interpretation A2.1:** OS at six months was similar for all therapies (range 95-100%), except for 'Other' (88%). There were no statistically significant differences except for ibrutinib versus Other (p=0.04).

**Conclusion A2.1**: Reject the hypothesis, as all CLL treatments, except for Other, had similar OS rates at six months.

***Hypothesis A2.2: OS at six months will be higher with NA than CT/CIT treatments.***

**Strategy A2.2:** Limit the study population to only those patients who had at least 6 months of follow-up. Determine and compare OS at six months for patients on NA and CT/CIT using the chi-square statistic. Call p-values less than 0.05 statistically significant.

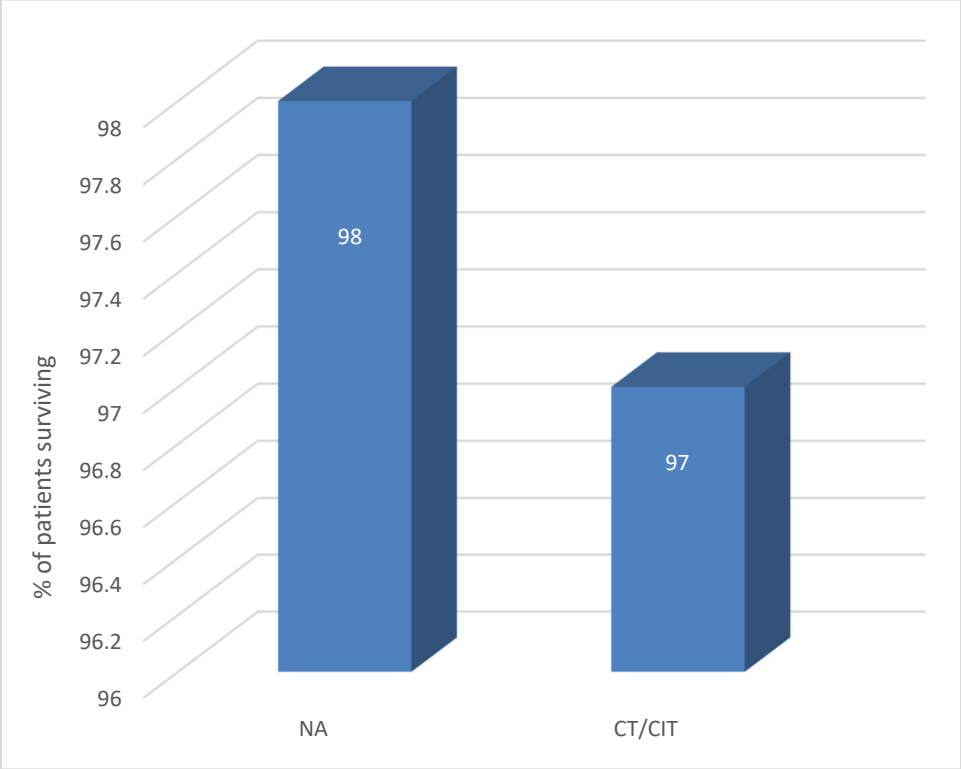



**Figure 4.8** OS at six months for NA and CT/CIT treatments **(A2.2.)**

**Interpretation A2.2:** OS at six months was similarly high for patients on NA (97.9%) and CT/CIT (97.1%) treatments, p=0.052.

**Conclusion A2.2:** Reject the hypothesis as OS at six months was statistically similar for patients on NA and CT/CIT treatments.

**Aim 3: Determine and compare OS, as a timed outcome, for patients on NA and CT/CIT.**

***Hypothesis A3.1: OS will be higher with NA than CT/CIT treatments.***

**<u>Strategy A3.1</u>:** Construct survival curves for patients on NA and CT/CIT using the Kaplan Meier Method. Compare the curves using the Log Rank test. Call p-values less than 0.05 statistically different.

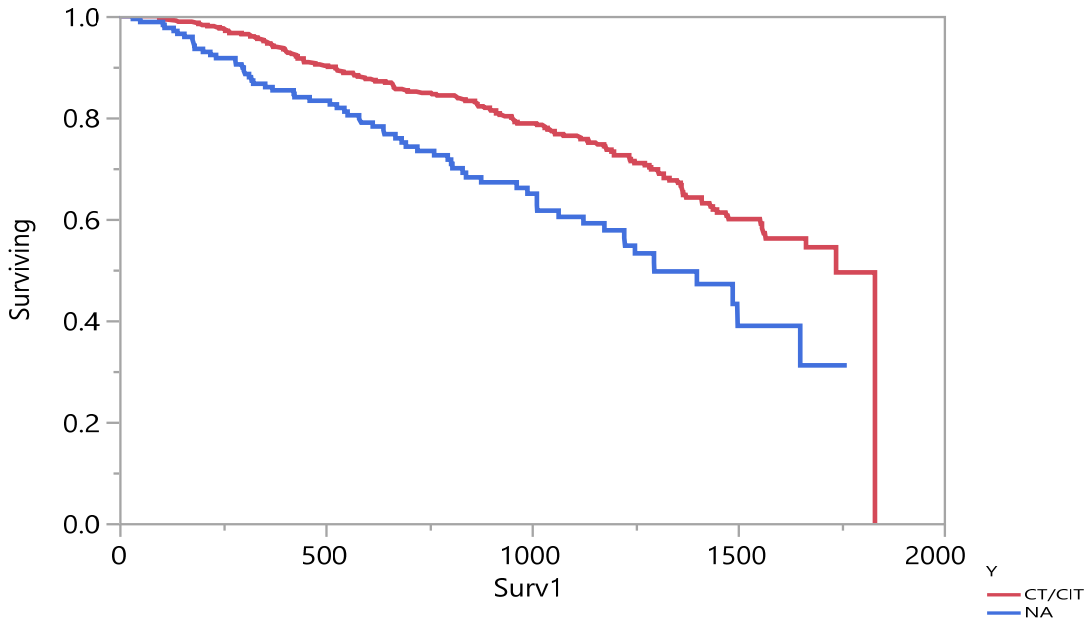



**Figure 4.9** Survival Analysis curves for NA and CT/CIT from treatment initiation to all-cause death. **(A3.1.)**

**Interpretation A3.1:** Survival times were higher for patients on CT/CIT treatments than for those on NA and the difference was statistically significant ($p<0.0001$).

**Conclusion A3.1:** Reject the hypothesis, as survival times were higher for patients on CT/CIT as compared to patients on NA.

**Aim 4: Determine time from diagnosis to treatment initiation (TTFT), time from initiation to discontinuation (TIDC), and time to next treatment (TTNT), for the nine select therapies.**

***Hypothesis A4.1: Time to first treatment (TTFT), time from initial treatment to discontinuation (TIDC), and time-to-next treatment (TTNT), will be similar for all select nine therapies.***

**Strategy A4.1*:*** Calculate the mean ± standard deviation for each timed outcome for the nine select therapies. Compare and determine if there are any differences using student t-test with ibrutinib as reference group.

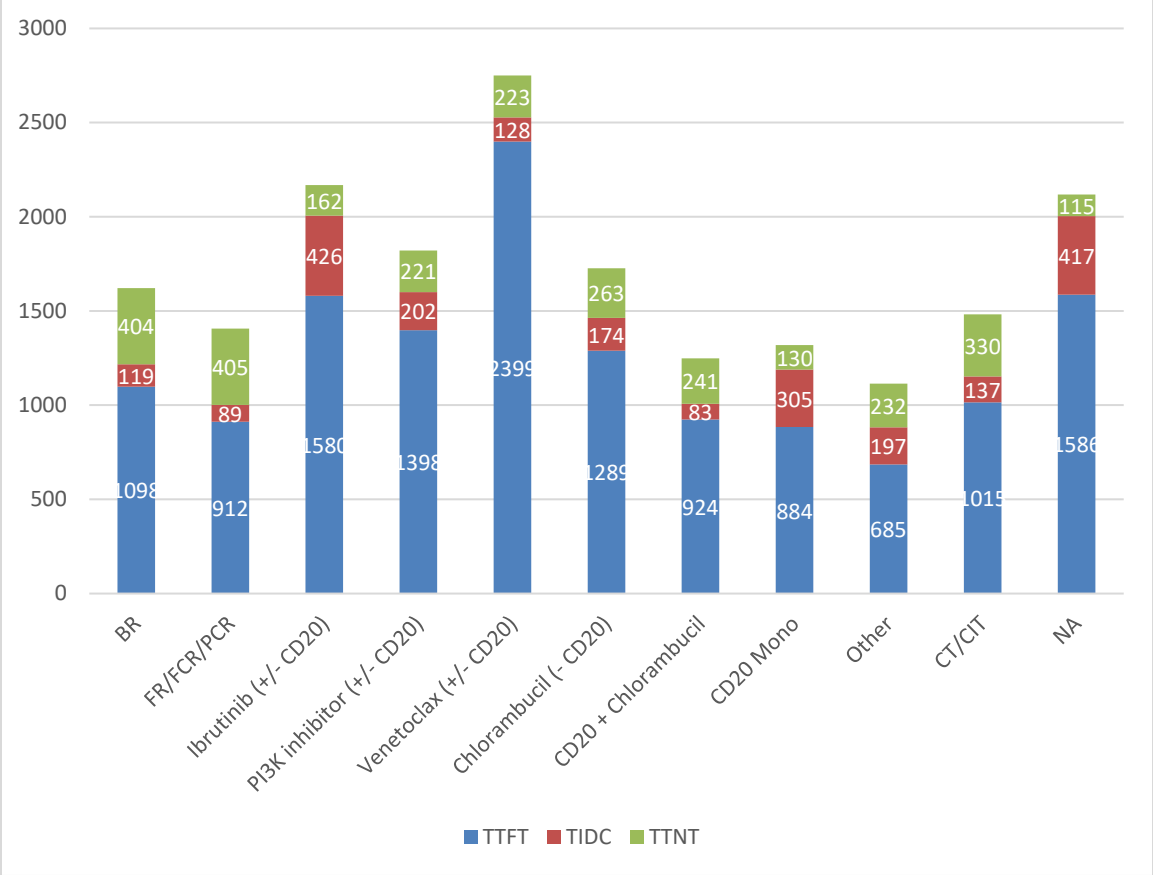



**Figure 4.10** Time-based treatment outcomes (TTFT, TIDC, TTNT) for nine select therapies **(A4.1.)**

| Therapies | Treatment Outcome (Days) | | | | | |
|---|---|---|---|---|---|---|
| | TTFT ± Stdev | P-value (95%CI) | TIDC ± Stdev | P-value (95%CI) | TTNT ± Stdev | P-value (95%CI) |
| BR | 1098 ± 1133 (n=167) | 0.001* (197.872, 782.128) | 119 ± 177 (n=167) | <0.00001* (235.7026, 378.2974) | 404 ± 361 (n=159) | < .00001* (-310.1964, -173.8036) |
| FR/FCR/PCR | 912 ± 1089 (n=75) | 0.0002* (325.4924, 1010.5076) | 89 ± 79 (n=87) | < 0.00001* (268.8661, 405.1339) | 405 ± 399 (n=86) | < .00001* (-336.5273, -149.4727) |
| IBRU | 1580 ± 1515 (n=160) | REF | 426 ± 434 (n=168) | REF | 162 ± 209 (n=115) | REF |
| PI3K | 1398 ± 1877 (n=4) | 0.8598 | 202 ±189 (n=4) | 0.1116 | 221 ± 244 (n=4) | 0.6656 |
| VEN | 2399 ± 544 (n=2) | 0.291 | 128 ± 177 (n=2) | 0.261 | 223 ± 42 (n=2) | >.99999 |
| CHLOR | 1289 ± 1249 (n=115) | 0.0826 | 174 ± 269 (n=121) | < 0.00001* (170.4893, 333.5107) | 263 ± 332 (n=113) | 0.0066* (-173.623, -28.377) |
| CD20+CHLOR | 924 ± 1003 (n=49) | 0.0006* (287.2517, 1026.7483) | 83 ± 89 (n=50) | < 0.00001* (272.4697, 413.5303) | 241±346 (n=49) | 0.142 |
| CD20 MONO | 884 ± 1071 (n=28) | 0.0048* (223.1417, 1168.8583) | 305 ± 412 (n=31) | 0.1436 | 130 ± 221 (n=26) | 0.5052 |
| OTHER | 685± 983 (n=17) | 0.0026* (343.3381, 1444.6619) | 158 ± 255 (n=25) | < 0.00001* (145.267, 390.733) | 232 ±336 (n=9) | 0.5552 |

**Table 4.1.** Comparative Analysis of Treatment outcomes (TTFT, TIDC and TTNT) for all nine Therapies. **(A4.1)**

**Interpretation A4.1:**

- Of all nine 1L therapies, venetoclax had the longest TTFT followed by ibrutinib and the PI3K therapy, but these were not statistically significant when compared with ibrutinib.
- TTFT for all chemoimmunotherapies were significantly different from that of ibrutinib except for chlorambucil.
- Among the chemoimmunotherapies, chlorambucil had the longest TTFT followed by BR, CD+Chlor and FC/FCR/PCR therapies in descending order.
- Ibrutinib had the longest TIDC of all nine therapies, followed by CD monotherapy ($p<0.00001$), PI3K, and venetoclax.
- The chemoimmunotherapies tended to have shorter TIDC that were significantly different ($p<0.00001$) from that of ibrutinib except for the CD 20 monotherapy.
- TTNT was longest for FC/FCR/PCR and BR chemoimmunotherapies, followed by chlorambucil, CD 20+Chlor, venetoclax and PI3K.
- Ibrutinib had the shortest TTNT next to CD 20 monotherapy. Only the values for FC/FCR/PCR, BR and chlorambucil were significantly different statistically from that of ibrutinib.

**Conclusion A4.1:** BR and FR /FCR/PCR have the longest TTNT indicating longer remission before next therapy. They also have the shortest TIDC. Reject the hypothesis because all three timed outcomes were different for all therapies.

***Hypothesis A4.2: Time to first treatment (TTFT), time from initial treatment to discontinuation (TIDC), and time-to-next treatment (TTNT), will be longer for novel agents than with CT/CIT.***

**Strategy A4.2:** Calculate the mean ± standard deviation for each timed outcome for the CT/CIT and NA treatments, respectively and determine if there are any differences between the two treatment groups using Student's t-test.

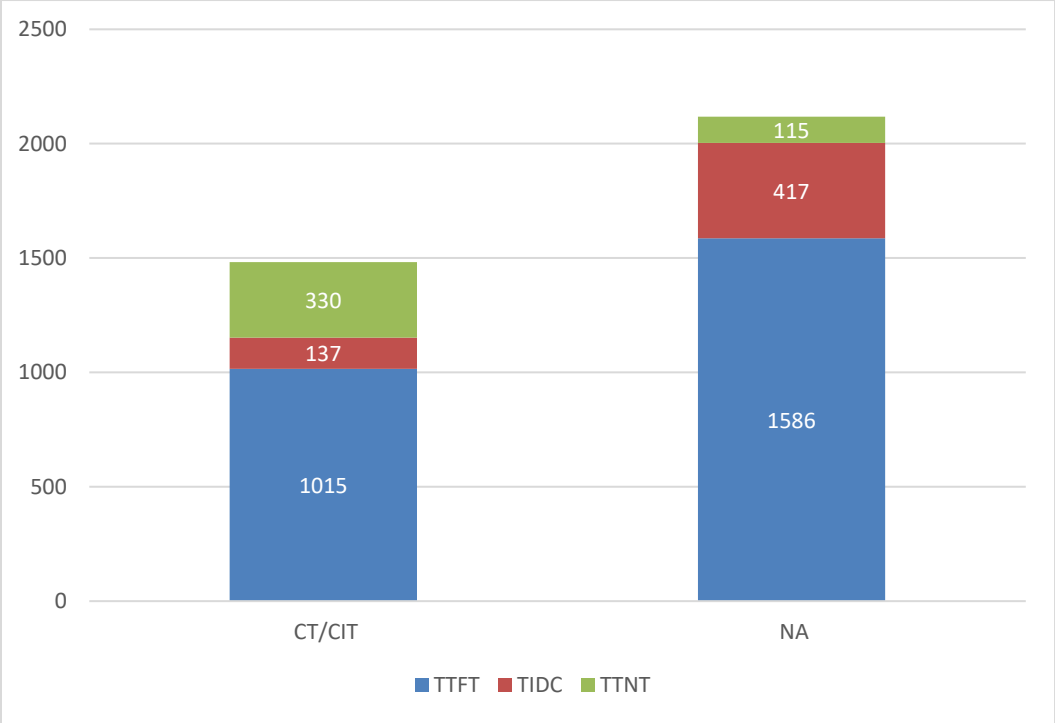



**Figure 4.11** Time-based treatment outcomes (TTFT, TIDC, TTNT) for CT/CIT and NA **(A4.2.)**

| Therapies | TTFT ± Stdev | TIDC ± Stdev | TTNT ± Stdev |
|---|---|---|---|
| CT/CIT | 1015 ± 1138 (n=473) | 137 ± 219 (n=481) | 330 ± 358 (n=481) |
| Novel Agents | 1586 ± 1500 (n=166) | 417 ± 429 (n=174) | 115 ± 189 (n=174) |
| P-value (95%CI) | 0.00001 (318.5351, 821.4649) | < 0.00001 (-347.072, -212.928) | < 0.00001 (145.3403, 230.6597) |

**Table 4.2.** Comparative Analysis of Treatment outcomes (TTFT, TIDC and TTNT) for CT/CIT and NA Therapies. **(A4.2)**

**Interpretation A4.2:** The CT/CIT treatments had shorter TTFT than the NA treatments, and this was statistically significant ($p<0.0001$). The NA treatments had significantly longer TIDC and shorter TTNT than the CT/CIT treatments.

**Conclusion A4.2:** Accept hypothesis for TTFT and TIDC, and reject it for TTNT.

**Aim 5: Determine and compare health care facility utilization (emergency room visits, urgent care visits, hospital admissions) at 6 months post therapy initiation and end of study periods, for CT/CIT and NA**.

***Hypothesis A5.1: A higher proportion of patients on CT/CIT than those on NA therapies will have emergency room visits, urgent care visits, and hospital admissions at six months post therapy initiation.***

**Strategy A5.1:** Determine and compare the proportions of patients who utilized each facility-based care within six months of therapy initiation for the two treatment groups using chi square test. $P<0.05$ is statistically significant.

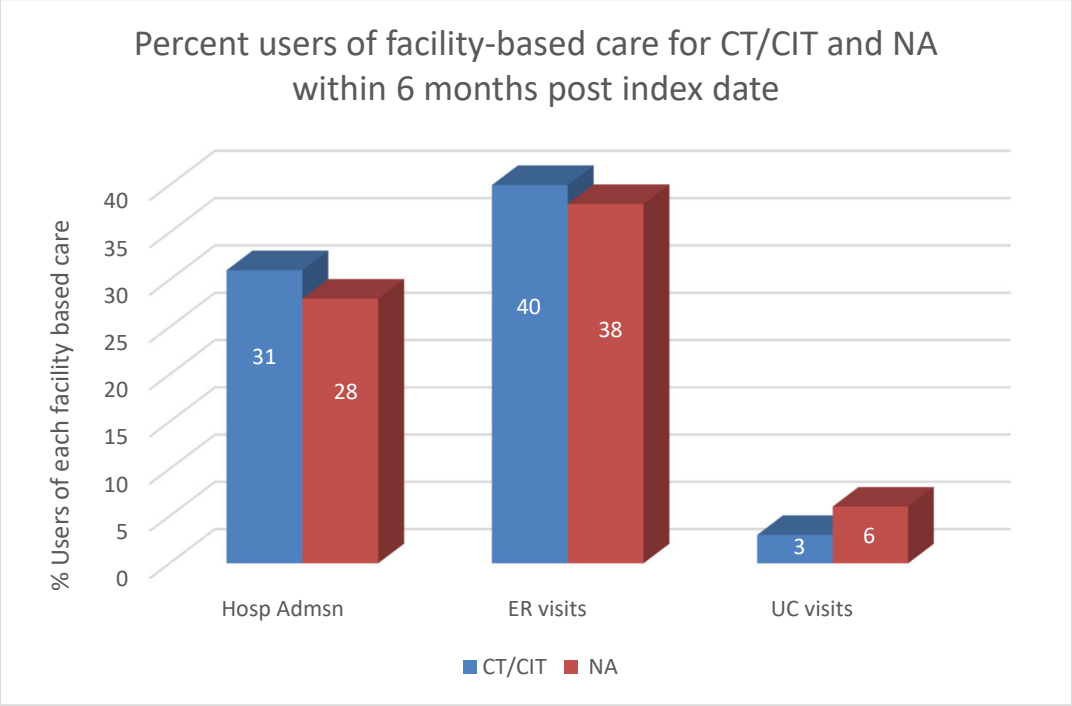



**Figure 4.12** Hospital admissions, Emergency room visits, and Urgent Care visits for CT/CIT and NA Therapies at 6 months post index date. **(A5.1.)**

***Hypothesis A5.2: At the end of study period, a higher proportion of patients on CT/CIT than those on NA therapies will have emergency room visits, urgent care visits, and hospital admissions.***

**Strategy A5.2:** Determine and compare the proportions of patients who utilized each facility-based care for the two treatment groups using chi square test. $P<0.05$ is statistically significant.

| Therapy | Treatment outcome | | |
|---|---|---|---|
| | Hosp Admsn | ER visits | UC visits |
| CT/CIT | 328/481 (68%) | 353/481(73%) | 50/481 (10%) |
| NA | 106/174 (61%) | 111/174 (64%) | 19/174 (11%) |
| P-value | 0.0821 | 0.0170 | 0.8469 |

**Table 4.3** Comparative Analysis of utilization of health facility-based care (hospital admissions emergency room visits, urgent care visits,) for CT/CIT and NA Therapies at end of study period. (A**5.2.)**

**Interpretation A5.1 and A5.2:** At the 6 months mark, there was no significant difference in healthcare utilization between the two treatment groups. At the end of the study period however, hospital admissions and ER visits were higher with the CT/CIT when compared with the novel agents; however, only the ER visits was significantly different. UC visits were similar.

**Conclusion A5.1and A5.2:** CT/CIT is associated with higher ER visits and a tendency towards higher hospital admissions than the novel agents.

**Aim. 6: Determine and compare the pattern of select complications after 6 months of treatment in patients initiated on each of the nine select therapies.**

***Hypothesis A6.1: There will be no difference in the pattern of select complications between the nine CLL therapies.***

**Strategy A6.1:** Limit the population to those who had any of the select seven complications at 6 months of treatment. The proportions of patients who had each of the seven select complications were determined for each 1L therapy. Chi square was used to

check for statistically significant differences in the most prevalent complication among the therapies using ibrutinib as reference

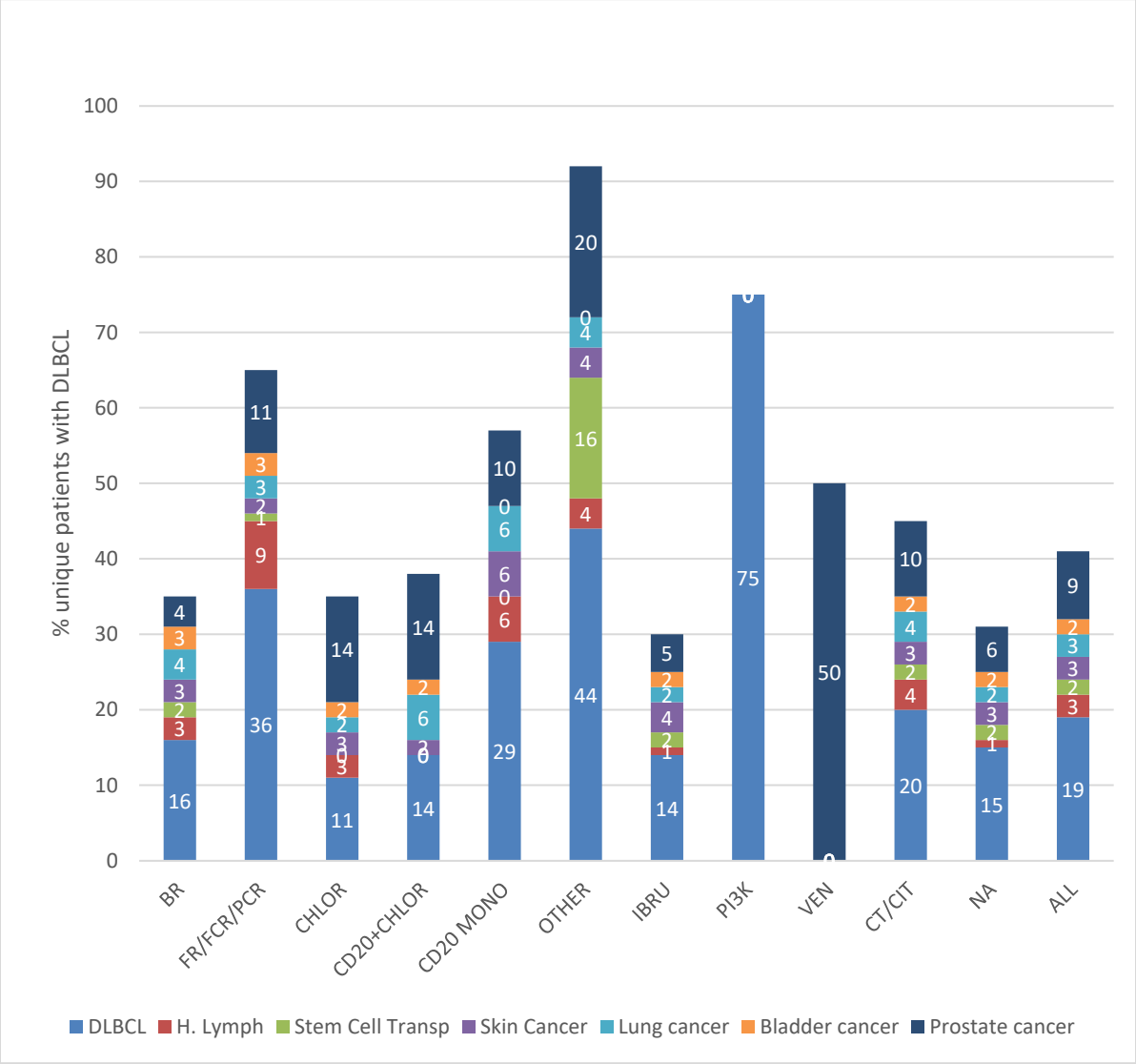



**Figure 4.13** Distribution of select complications in the nine therapies and 'overall'. **(A6.1)**

**Interpretation A6.1**

- The percentage of select clinical conditions seen after six months of therapy initiation are diffuse large B-cell lymphoma (19%), hodgkin's lymphoma (3%), stem cell transplant (2%), skin cancer (3%), lung cancer (3%), bladder cancer (2%) and prostate cancer (9%).
- Within each of the nine select therapies, diffuse large B-cell lymphoma (DLBCL) was the most frequent complication, followed by prostate cancer.
- DLBCL significantly higher compared to that in ibrutinib was seen in the PI3K (75%, p=0.02), the group "OTHER" (44%, p=0.0002), FR/FCR/PCR (36%, p=0.00005), and CD20 monotherapy (29%, p=0.033).
- In venetoclax and chlorambucil patients, prostate cancer was more prevalent than DLBCL. Prostate cancer occurrence was significantly more in therapies "OTHER" (20%, p=0.022), CHLOR (14%, p=0.011) and CD20+CHLOR (14%, p=0.011), with reference to ibrutinib.
- Stem cell transplant was seen most in the "OTHER" therapy and vaguely present in the rest of the therapies.

**Conclusion A6.1:** Diffuse large B-cell lymphoma (DLBCL), was the most prevalent complication for most therapies, occurring as 75% of all complications in FR/FCR/PCR and PI3K each, 58% (CD 20 + Chlorambucil), 46% (BR), 48% (OTHER), 47% (Ibrutinib), 45% (CD20 Monotherapy), 31% in Chlorambucil, and 0% (venetoclax). Prostate Cancer was the most prevalent in other therapies. The occurrence of

complications was different in the different therapies, so hypothesis of no difference is rejected.

***Hypothesis A6.2: All the complications will be more prevalent in the CT/CIT therapies compared to the NA.***

**Strategy A6.2:** The proportions of patients who had complications were combined for ibrutinib, venetoclax and PI3K for each of the seven select complications to obtain the values for NA therapies. The proportions for all the other therapies were combined to create the CT/CIT group. Chi square was used to check for statistically significant differences between the two groups.

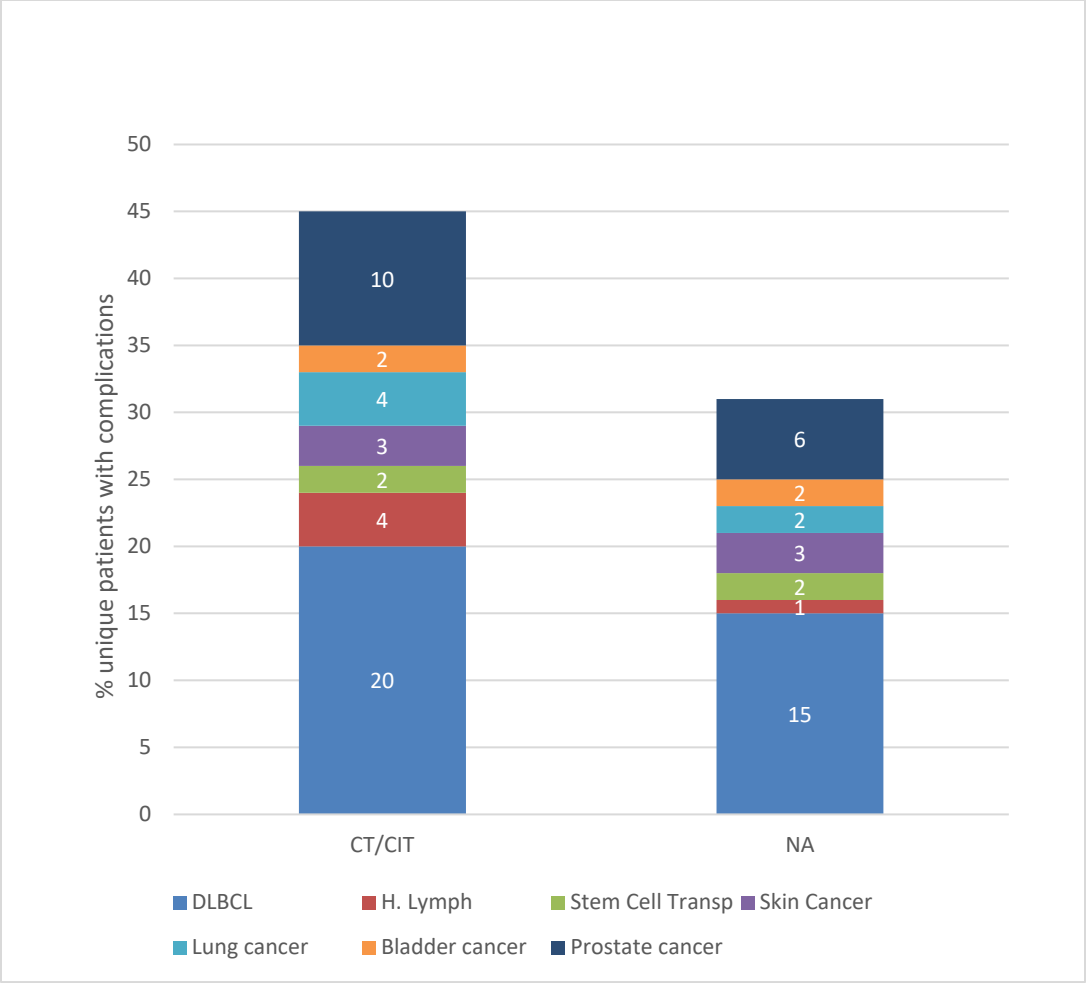



**Figure 4.14** Distribution of Select Complications in CT/CIT and NA Therapies. **(A6.2.)**

**<u>Interpretation A6.2</u>:**

- DLBCL was more prevalent in the CT/CIT category, when compared with the novel agents' group but this difference was not found to be statistically significant ($p = 0.1171$).
- Hodgkins lymphoma tended to be negligible in the NA category while it was prominent with the CT/CIT regimens, although the difference was not statistically significant ($p = 0.0591$).

**Conclusion A6.2:** The two most frequent complications (DLBCL, prostate cancer) were more prevalent in the CT/CIT treatments than the NA treatments. The select complications were either similar in both the CT/CIT and NA treatmentss or tended to be more prevalent in the traditional chemoimmunotherapies (CT/CIT) than the novel agents. Null hypothesis of no difference is rejected.

***Hypothesis A6.3: There will be no difference in the proportion of patients with DLBCL complication between those on FC/FCR/PCR and ibrutinib.***

**Strategy A6.3:** The proportions of patients who had DLBCL were determined for FC/FCR/PCR and ibrutinib and compared using chi square.

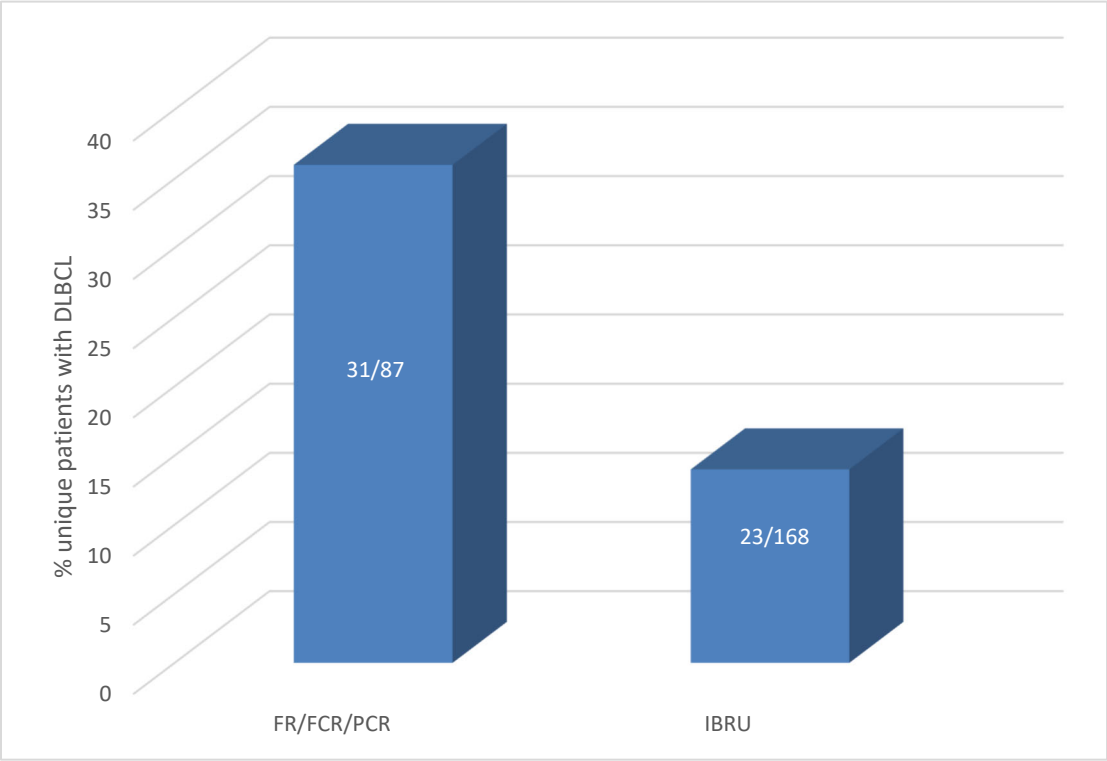



**Figure 4.15** Proportion of patients on FC/FCR/PCR and Ibrutinib with DLBCL (**A6.3.)**

**Interpretation A6.3:** Relative to ibrutinib (14%), FC/FCR/PCR had more than twice the percentage of cases of DLBCL (35%, p= 0.0005).

**Conclusion A6.3:** Patients on ibrutinib experienced less of DLBCL when compared with those on FC/FCR/PCR, so the null hypothesis of no difference is rejected.

**Aim 7: Describe and compare the uptake of 1L CT/CIT and NA therapies for black and white patients.**

***Hypothesis 7A.1: The black patients will lag behind in the uptake of novel therapies versus the white patients.***

**Strategy A7.1:** Determine the uptake of all nine therapies in the 1L for years 2014 -2017, for black and white patient populations. Compare the proportions using chi square test.

| | 2014 | | 2015 | | 2016 | | 2017 | | All Years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | P-value |
| | W | B | W | B | W | B | W | B | W | B | |
| | n=181 | n=30 | n=158 | n=26 | n=102 | n=18 | n=75 | n=14 | 516 | 88 | |
| *BR* | 31% | 33% | 28% | 38% | 22% | 22% | 19% | 7% | 137(27%) | 25(28%) | 0.7160 |
| *FR/FCR/PCR* | 16% | 27% | 11% | 19% | 11% | 6% | 11% | 29% | 66(13%) | 18(20%) | 0.0548 |
| *CHLOR* | 16% | 23% | 20% | 15% | 20% | 11% | 19% | 21% | 95(18%) | 16(18%) | 0.9591 |
| *CD20+CHLOR* | 7% | 3% | 10% | 12% | 11% | 6% | 5% | 0% | 43(8%) | 5(6%) | 0.3953 |
| *CD20 MONO* | 7% | 33% | 4% | 0% | 3% | 6% | 4% | 14% | 25(5%) | 4(5%) | 0.9033 |
| *OTHER* | 3% | 0% | 3% | 4% | 3% | 28% | 4% | 0% | 16(3%) | 6(7%) | 0.0853 |
| *IBRU* | 20% | 3% | 22% | 12% | 30% | 22% | 37% | 29% | 129(25%) | 12(14%) | 0.0198 |
| *P13K* | 0% | 0% | 2% | 0% | 1% | 0% | 0% | 0% | 4(0.7%) | 0(0%) | |
| *VEN* | 0% | 0% | 0% | 0% | 0% | 0% | 1% | 0% | 1(0.2%) | 0(0%) | |
| *CT/CIT-OTHER* | 80% | 97% | 77% | 88% | 69% | 78% | 61% | 71% | 382(74%) | 76(86%) | 0.0125 |
| *Novel Therapies* | 20% | 3% | 23% | 12% | 31% | 22% | 39% | 29% | 134(26%) | 12(14%) | 0.0125 |

**Table 4.4** Uptake of the 1L therapies by White and Black Patients (2014 – 2017). **(A7.1.)**

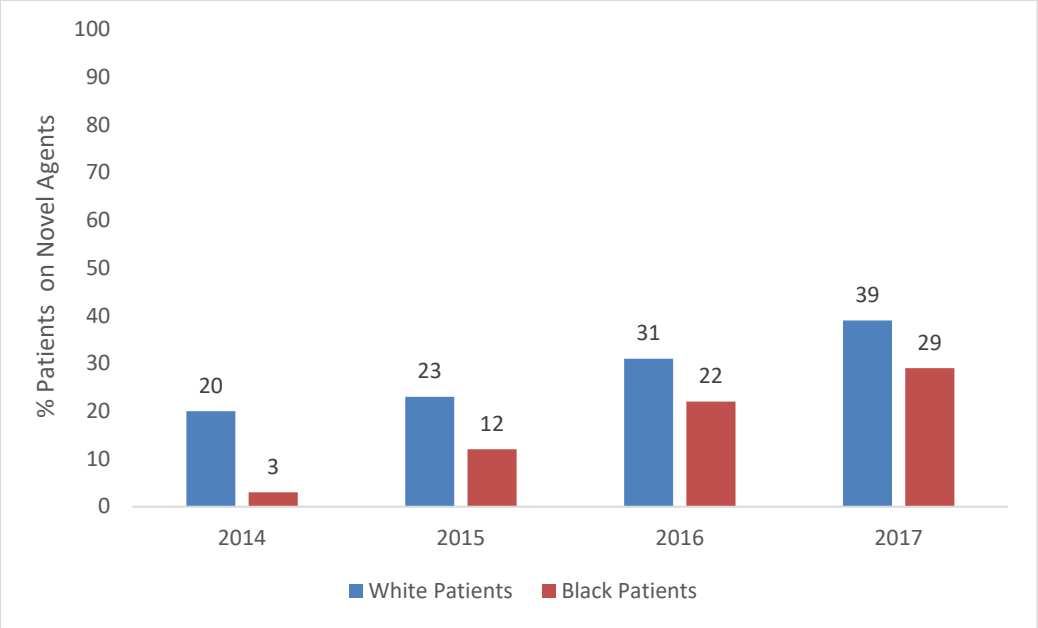



**Figure 4.16** Comparison of Novel Therapy Uptake by Black and White Race. **(A7.1.)**

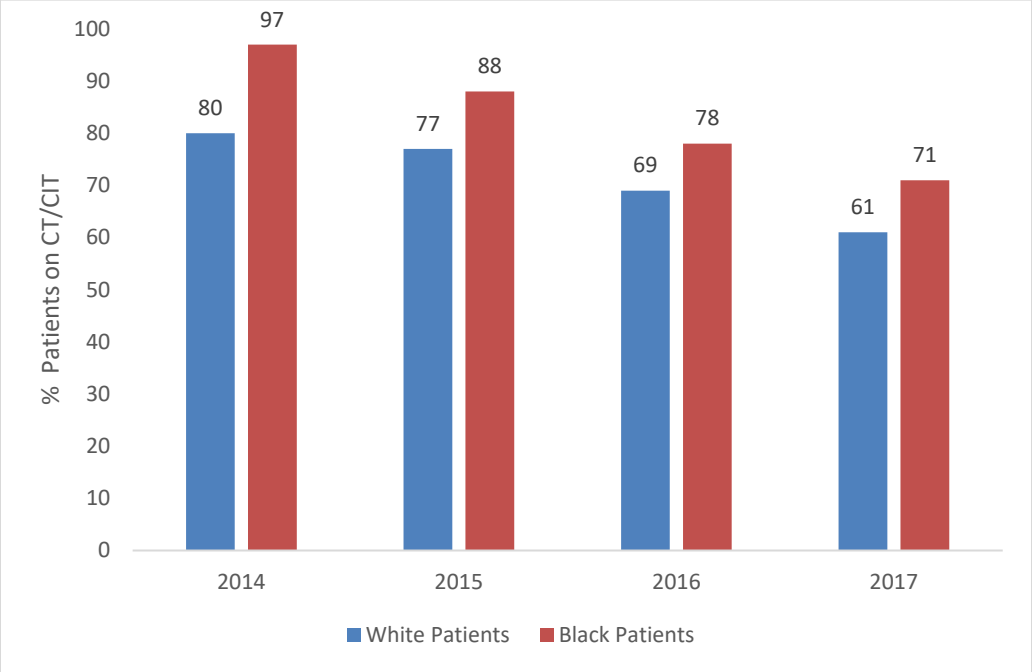



**Figure 4.17** Comparison of CT/CIT uptake by Black and White Race. **(A7.1.2.)**

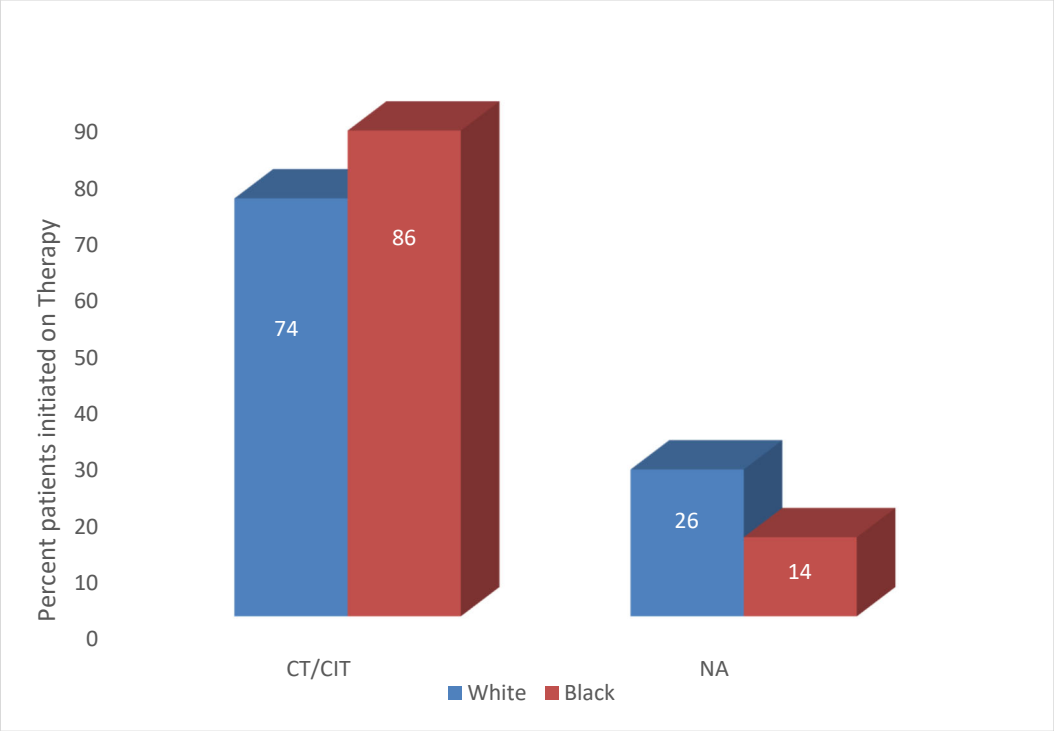



**Figure 4.18** Comparison of 'all year' CT/CIT and NA uptake by Black and White Race. **(A7.1.3.)**

**<u>Interpretation A7.1</u>:**

- For all therapies, chi square test showed no significant difference in use between white and black patients for the years 2014 – 2017 (see table A7.1), except for ibrutinib.
- Ibrutinib was received more by white than black patients ($p = 0.0198$).
- FC/FCR/PCR showed a tendency towards predominance use in black patients compared to the white patients although not statistically significant ($p = 0.0548$).

- For NA group, in 2014, 20% of white patients and 3% of black patients received novel agents (difference of 17%, p=0.03). This gap persisted for all study years: 2015 (23% vs. 12%, gap of 11%, p=0.17), 2016 (31% vs. 22%, gap of 9%, p=0.43), and 2017 (39% vs. 29%, gap of 10%, p=0.47), though not statistically significant (likely due to limited sample size).
- More black patients than whites received CT/CIT each year between 2014 – 2017. The difference in uptake of CT/CIT between the black and white patients were 17% (2014), 11% (2015), 11% (2016) and 10% (2017) respectively.
- Comparing the combined four-year (2014 – 2017) use, the traditional chemotherapy/chemoimmunotherapy (CT/CIT) tended to be more common among the black patients than the whites (p = 0.0125), while the novel agents use was more likely in whites (p = 0.0125).

**Conclusion A7.1** The use of CT/CIT and NA for black and white patients, a significant relationship with race was observed. On yearly basis, the black patients lagged behind the whites in uptake of the novel agents. Accept the hypothesis that black patients will lag behind in uptake of novel agents.

**Aim 8: Determine if CT/CIT and NA use is different for the age groups <65 years, 65-74 years and >74 years.**

***Hypothesis 8: CT/CIT and NA use will be similar for all age groups.***

**Strategy A8.1:** Create three age-based groups (<65 years, 65-74 years and >74 years) for each of NA and CT/CIT treatments. Determine the proportion of patients on CT/CIT and NA respectively for each age-group.

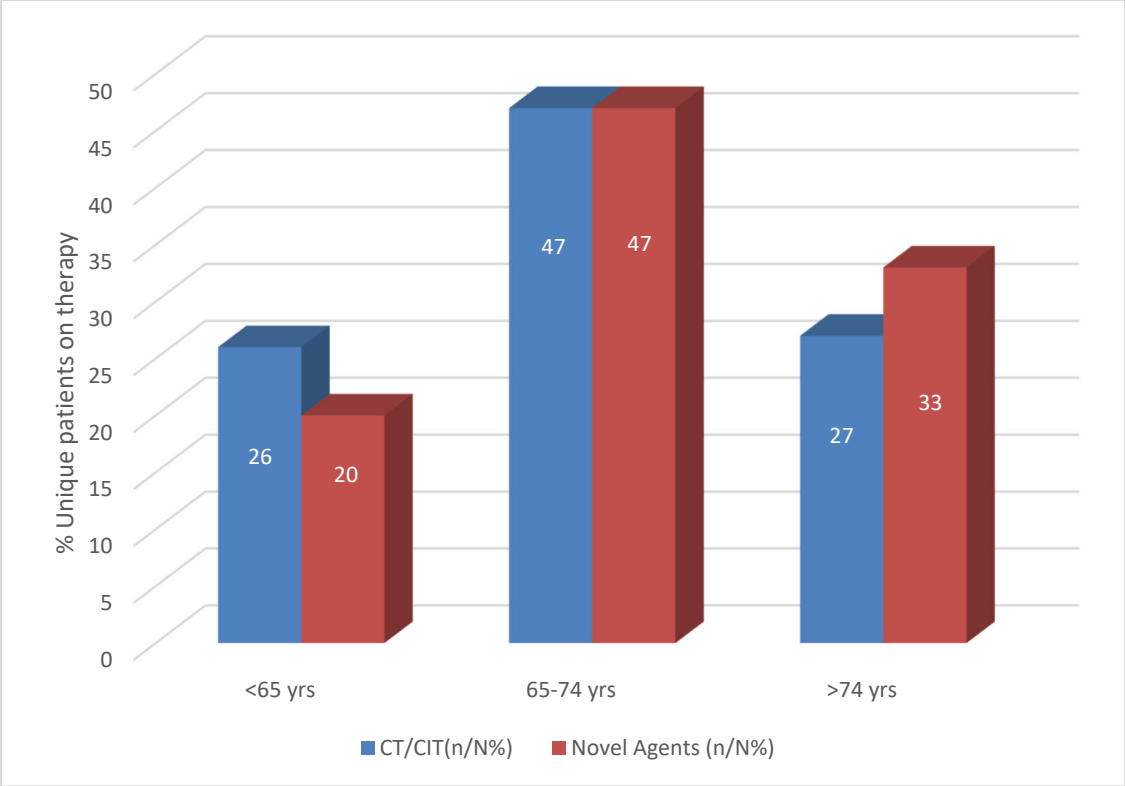



**Figure 4.19** Use of CT/CIT and NA use in different Age-groups. **(A8.1.)**

**Interpretation A8.1:**

- In the younger age group (<65 years), the CT/CIT was more predominantly used compared to the NA.

- The novel agents had a higher uptake in the oldest population (>74 years) compared to CT/CIT.
- In the age-group in between both classes of therapies were similar in uptake.

**Conclusion A8.1:** The 6% difference between both classes of therapies in the youngest (p = 0.071) and oldest age groups (0.145), though not statistically significant, may be important clinically. Accept the hypothesis that use of CT/CIT and NA treatments are similar in all age groups.

**Aim 9: Determine if FC/FCR/PCR and ibrutinib use and uptake is different for age groups (<65 years, 65-74 years and >74 years).**

***Hypothesis 9A.1:*** **FCR and ibrutinib use will not be different within each age group.**

**Strategy A9.1:** Determine the proportion of patients on FC/FCR/PCR and ibrutinib respectively, within the three age groups (<65 years, 65-74 years and >74 years). Compare differences using chi square test.

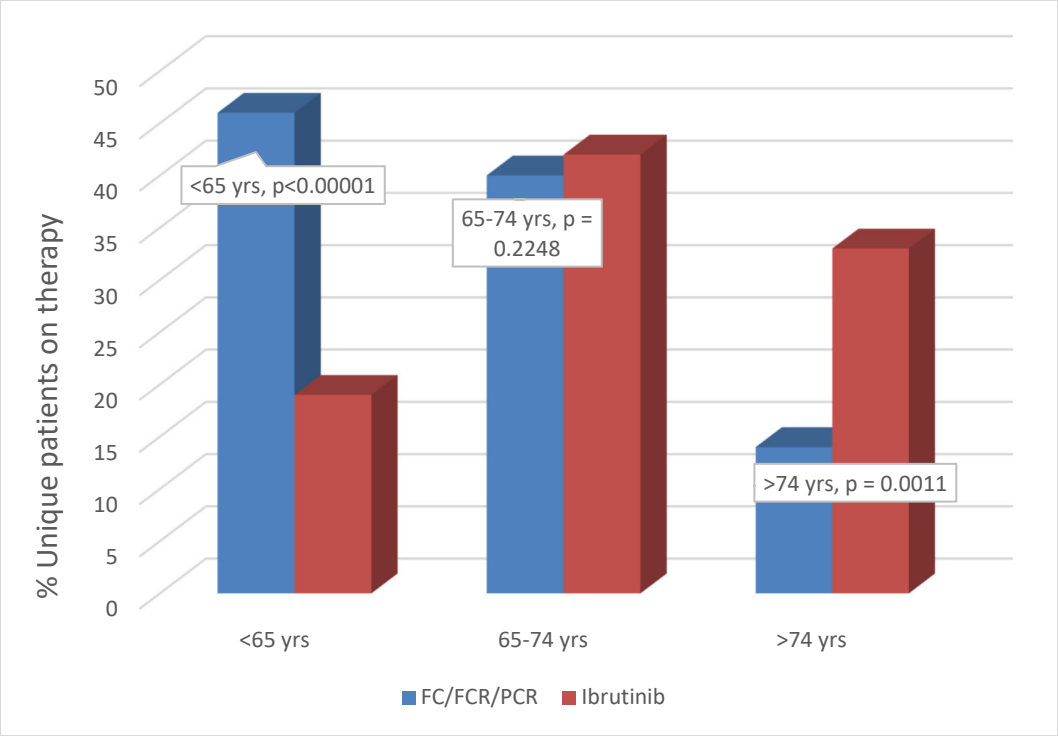



**Figure 4.20** Use of FC/FCR/PCR and Ibrutinib in age groups (<65 years, 65-74 years and >74 years). **(A9.1.)**

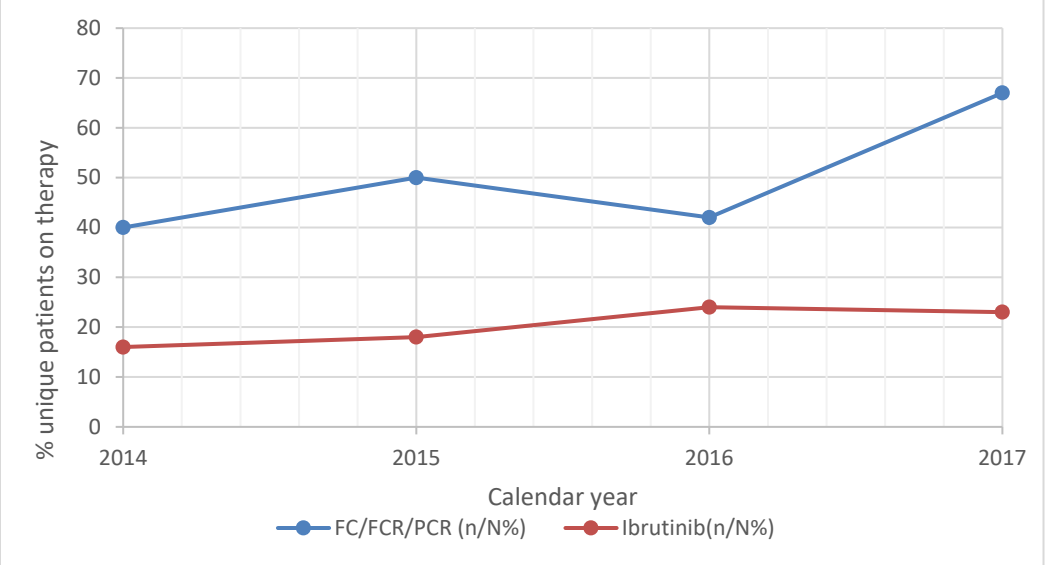



**Figure 4.21** Uptake of FC/FCR/PCR and Ibrutinib in youngest age group (<65 years). **(A9.1.2.)**

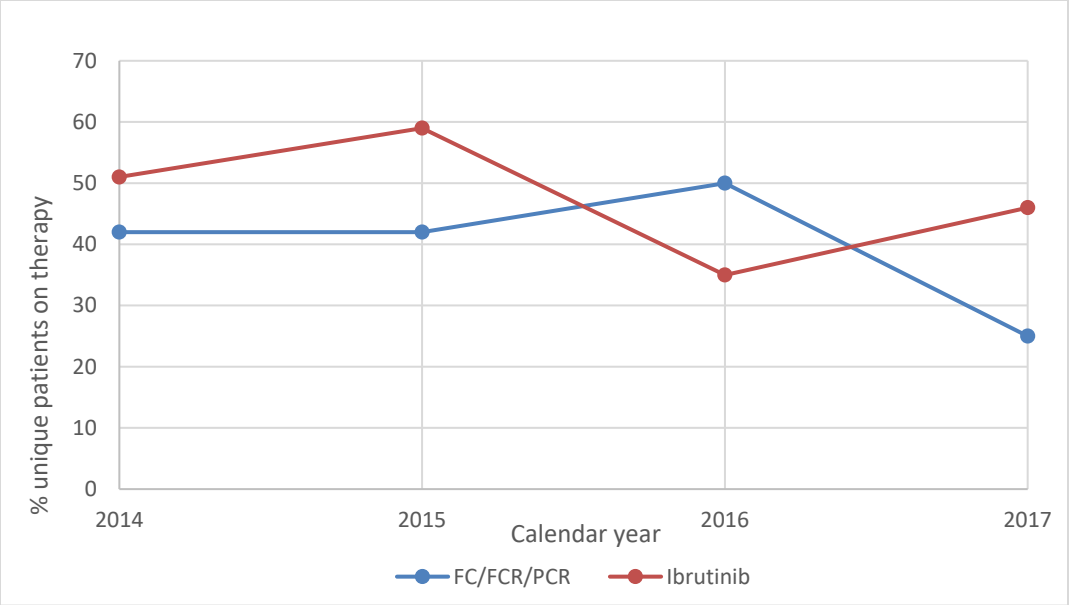



**Figure 4.22** Uptake of FC/FCR/PCR and Ibrutinib in Patients 65 - 74 years. **A9.1.3.**

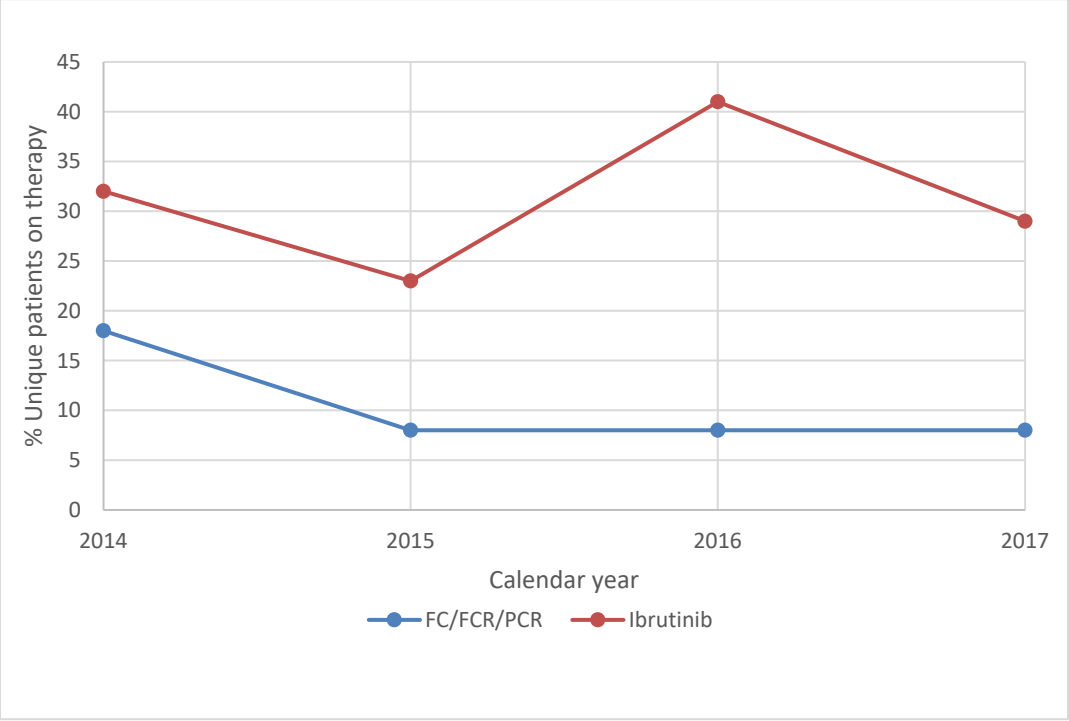



**Figure 4.23** Uptake of FC/FCR/PCR and Ibrutinib in older Patients (>74 years). **(A9.1.4.)**

**Interpretation A9.1:**

- FC/FCR/PCR uptake was higher in the youngest age-group (<65 years) when compared with ibrutinib, with a usage ratio greater than 2:1, and the gap was maintained throughout the years studied; 2014 (24%), 2015 (35%), 2016 (18%), and 2017 (57%).
- In age-group of 65-74 years old patients, the use of FC/FCR/PCR and ibrutinib did not show a distinct pattern though the uptake of ibrutinib tended to be higher over the years studied.
- In the oldest age-group (>74 years), the difference in uptake between the two therapies is approximately a 100% in favor of the novel agents ($p = 0.0011$), with an overall upward trend.

**Conclusion A9.1:** The uptake of FC/FCR/PCR maintained a significant lead over the novel agent ibrutinib, for the years studied, rejecting the null hypothesis. The introduction of ibrutinib did not negatively impact the use of purine analogue -based regimen FC/FCR/PCR in the younger patients.

In the group of 65-74 years old patients, age did not seem to influence which of the two therapies was used. Null hypothesis is accepted.

For the oldest patients' group, ibrutinib was used more than FC/FCR/PCR, rejecting the null hypothesis.

**Aim10: Compare use of FCR and ibrutinib for black and white patients in the different age groups.**

***Hypothesis A10.1: There will be no difference in the use of FCR and ibrutinib for black and white patients in the different age groups.***

**Strategy A10.1:** Determine the proportion of white and black patients initiated on FC/FCR/PCR and ibrutinib respectively for each age group. Compare differences in the use of both therapies between the races in each age group.

| | % Uptake of therapy (A) | | | % representation in sub-cohort (B) | | |
|---|---|---|---|---|---|---|
| FC/FCR/PCR | white | Black | p-value | White | Black | p-value |
| Age-group 1 | 25/39 (64%) | 14/39 (36%) | 0.013 | 25/117 (21%) | 14/40 (35%) | 0.085 |
| Age-group 2 | 31/35 (91%) | 3/35 (9%) | <0.00001 | 31/267 (12%) | 3/36 (8%) | 0.559 |
| Age-group 3 | 11/12 (92%) | 1/12 (8%) | 0.000045 | 11/164 (7%) | 1/16 (1%) | 0.944 |
| Ibrutinib | | | | | | |
| Age-group 1 | 24/31 (75%) | 7/31 (25%) | 0.000016 | 24/117 (21%) | 7/40 (18%) | 0.679 |
| Age-group 2 | 75/78 (96%) | 3/78 (4%) | <0.00001 | 75/267 (28%) | 3/36 (8%) | 0.011 |
| Age-group 3 | 47/52 (90%) | 5/52 (10%) | <0.00001 | 11/164 (7%) | 5/16 (31%) | 0.000992 |

**Table 4.5** Uptake of FR/FCR/PCR vs IBRU by age groups and race. **(A10.1.)**

**Interpretation A10.1:**

In the youngest age group (<65 years);

- 21% of white patients received FC/FCR/PCR and 21% received ibrutinib

- 35% of black patients aged <65 years received FC/FCR/PCR and 18% received ibrutinib.
- A difference of 14% exits between the black and white patients in the uptake of FC/FCR/PCR in favour of blacks, while the difference in uptake of ibrutinib is 3% in favour of whites.
- Therefore, black patients in the youngest age group were more likely to receive fludarabine-based therapies than their white counterparts, while white patients were more likely to receive ibrutinib than their black counterparts.

In the second age-group (65-74 years);

- 12% of white patients age (65 – 74 years) received FC/FCR/PCR, while 28% received ibrutinib.
- 8% of black patients age (65 – 74 years) received FC/FCR/PCR, while 8% received ibrutinib.
- Disparity is more prominent in this age group because the gap between white and black patients in the use of ibrutinib is 20% in favour of whites.

In the third age group (>74 years);

- 7% of white patients age (>74 years) received FC/FCR/PCR, while 7% received ibrutinib.
- 1% of black patients age (>74 years) received FC/FCR/PCR, while 31% received ibrutinib

*Further explanation:*

Table 10.1 shows two analyses (A and B), based on race for each sub-cohort of white and black patients. For each race, percentage use for each age-group (A) was also analyzed for its equivalent proportion in the whole cohort (B) for FC/FCR/PCR and ibrutinib. In all age groups, a statistically significant difference in uptake was observed between the white and black patients, however, when analysis was based on the proportional representation of each race in the whole cohort, most failed to be significant differences. For example, for FC/FCR/PCR, 64% of whites and 36% of Blacks were initiated on this therapy for the youngest age-group, a difference of 28% ($p= 0.013$).

Analyzing this uptake on the basis of proportional representation of whites and blacks in that age group in the cohort yielded 21% for whites and 35% for blacks and the difference was no longer statistically significant ($p= 0.085$) but there was a tendency for more black patients to receive the chemoimmunotherapy than white patients. There was no statistically significant difference in the proportional use of FC/FCR/PCR between the black and white patients in all age groups while for ibrutinib, the difference is significant for age-groups 2 and 3.

**Conclusion A10.1:** There is a disparity in the uptake of FC/FCR/PCR and ibrutinib between the black and white patients across all age groups. Black patients younger than75 years were less likely to receive ibrutinib. Accept hypothesis of no difference in use of FC/FCR/PCR and ibrutinib between blacks and whites in age group <65 years, reject it for age groups 65-74 and > 74 years old.

**Aim 11: Determine if 1L treatment patterns are different for patients in VA priority groups 1, 2-6, and 7-8.**

***Hypothesis A11.1: The use of all nine therapies will be similar for patients in all three VA priority groups.***

**Strategy A11.1:** Create three clusters of VA Priority Group numbers (1, 2-3, and 7-8). For each of the nine select therapies, assign patients to one of three clusters based on their VA priority group. Determine the proportion of patients in each of the three groups for each therapy. Compare the differences in proportions between groups 1 vs 2-3 and 1 vs 7-8 for each therapy, using chi square test.

| VA Priority Group | Proportion of CLL patients on 1L therapy |
|---|---|
| Group 1 | 258/655=39% |
| Groups 2-6 | 279/655=43% |
| Groups 7-8 | 118/655=18% |

**Table: 4.6** Distribution of CLL patients on 1L therapy in the VA Priority Groups. **(A11.1)**

| | VA Priority Group (n/N%) | | | | |
|---|---|---|---|---|---|
| Therapy | 1 | 2-6 | P-value | 7-8 | P-value |
| BR | 76/258 (29%) | 70/279 (25%) | 0.256 | 21/118 (18%) | 0.016* |
| FR/FCR/PCR | 36/258(14%) | 39/279 (14%) | 0.889 | 12/118 (10%) | 0.308 |
| IBRU | 68/258=26% | 66/279=24% | 0.470 | 34/118=29% | 0.619 |
| PI3K | 2/258=0.08% | 0/279=0% | | 2/118=2% | |
| VEN | 0/258=0% | 0/279=0% | | 2/118=2% | |
| CHLOR | 40/258=16% | 51/279=18% | 0.391 | 30/118=25% | 0.022* |
| ∗ CHLOR + CD20 | 17/258=7% | 26/279=9% | 0.244 | 7/118=6% | 0.809 |
| CD20 Mono | 9/258=3% | 14/279=5% | 0.382 | 8/118=7% | 0.154 |
| OTHER | 10/258=4% | 13/279=5% | 0.654 | 2/118=2% | 0.264 |
| ALL | 258/655=39% | 279/655=43% | | 118/655=18% | |
| CT/CIT | 188/258=73% | 213/279=76% | 0.355 | 80/118=68% | 0.313 |
| NA | 70/258=27% | 66/279=24% | 0.355 | 38/118=32% | 0.313 |

**Table: 4.7** Distribution of patients on the select nine therapies in the VA priority groups. (*P<0.05 with reference to priority group 1) **(A11.1.2)**

**Interpretation A11.1:** Uptake of all therapies was similar across all VA priority groups, except for BR (p=0.016) and Chlorambucil (p= 0.022), that were significantly different in priority group 7-8, compared to priority group 1.

**Conclusion A11.1:** Between the priority groups 1 and 2-3, there was little or no difference in the proportion of patients for each therapy. BR and Chlorambucil were more significantly used in the VA Priority group 1 than in groups 7-8.

***Hypothesis A11.2: The uptake of CT/CIT and NA therapies will be similar for patients in all three VA priority groups (1, 2-3, 7-8).***

**Strategy A11.2:** Create three clusters of VA Priority Group numbers (1, 2-3, and 7-8). For each of the nine select therapies, assign patients to one of three clusters based

on their VA priority group. For the NA category, patients on the novel agents (ibrutinib, PI3K and venetoclax) were combined in each of the three groups and their proportion determined. Patients on the remaining therapies were similarly combined and proportions determined for CT/CIT category. Compare differences for statistical significance at $p<0.05$, for groups 1vs 2-3 and 1vs 7-8 for CT/CIT and NA, using chi square test.

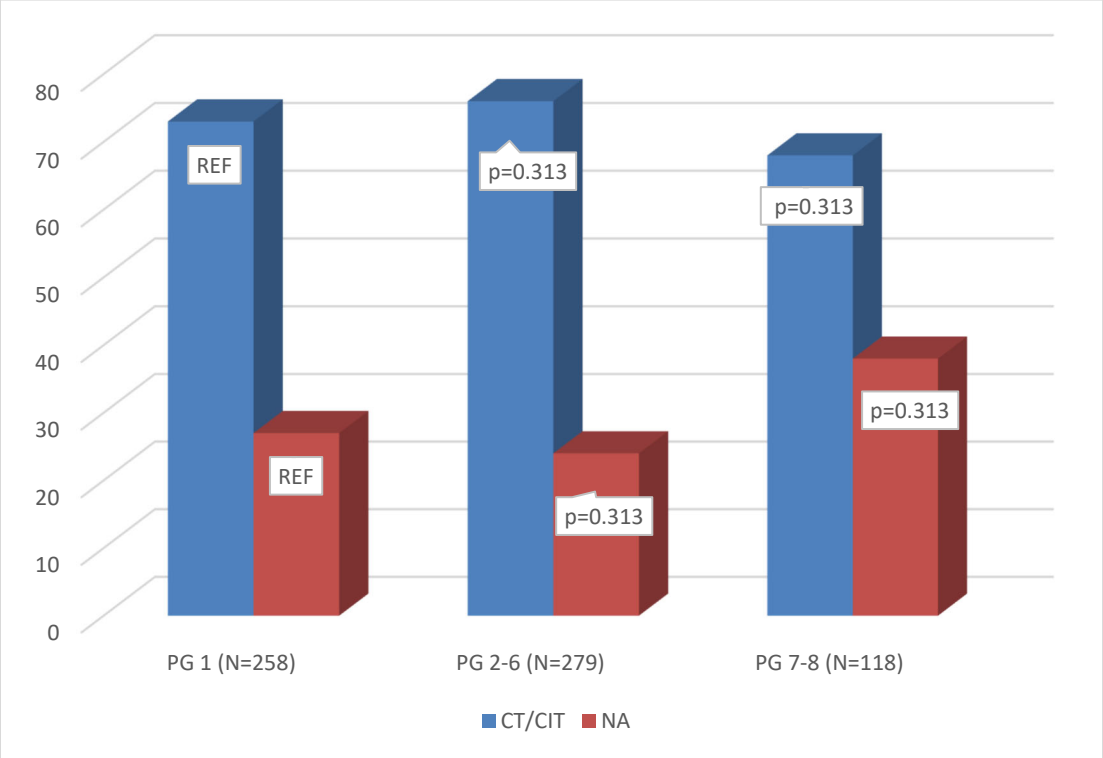



**Figure 4.24** Uptake of CT/CIT vs NA in the VA Priority groups **(A11.2.1.)**

| Therapy | VA Priority Group (n/N%) 1 | VA Priority Group (n/N%) 2-6 | P-value | VA Priority Group (n/N%) 7-8 | P-value |
|---|---|---|---|---|---|
| CT/CIT | 188/258=73% | 213/279=76% | 0.355 | 80/118=68% | 0.313 |
| I NA | 70/258=27% | 66/279=24% | 0.355 | 38/118=32% | 0.313 |
| P-value | <0.00001 | <0.00001 | | <0.00001 | |

n

**Table 4.8** Distribution of patients on CT/CIT and NA in the VA priority groups. **(A11.2.1.)**

**Interpretation A11.2:** The uptake of the novel agents is significantly lower than that of CT/CIT in all VA priority groups ($p<0.00001$). Although not statistically significant, the priority group 7-8, had the highest uptake of novel agents (32%), different from that of group 2-6 (24%) and group 1 (27%). Conversely, it had the lowest uptake in CT/CIT (68%) when compared to the other two clusters.

**Conclusion A11.2:** There was no significant difference in uptake of either CT/CIT or NA in the VA priority groups, though uptake of NA tended to be higher in the priority group 7-8.

**Aim 12: Determine the relationship between Charlson Comorbidity Index score and 6 months patient mortality.**

***Hypothesis 12.1: Charlson Comorbidity Index score will be higher in patients who die than in those who survive.***

**Strategy A12.1:** Create two groups of patients, one group comprising those dead within 6 months of treatment initiation and the second group comprising those who are alive. Determine the mean charlson age score for the two groups of patients for each therapy. Compare the average scores for both groups in all therapies.

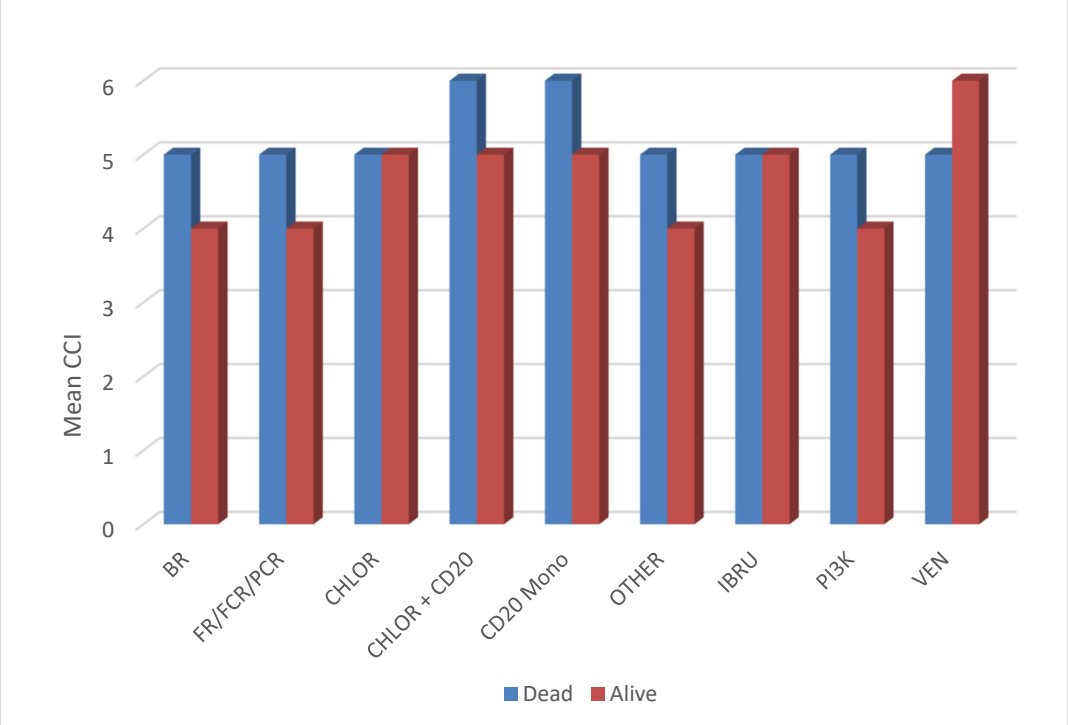



**Figure 4.25** Relationship between mean Charlson Age Score and 6-month mortality **(A12.1.)**

**Interpretation A12.1:**

- In all therapies except chlorambucil, ibrutinib and venetoclax, the mean charlson age scores tended to be higher for patients who were dead at 6 months (5-6), than for those who were alive (4-5), though this difference is small.
- For venetoclax, the average CCI score for the survivors at 6 months was higher than for the dead at six months.
- The average CCI scores for patients on chlorambucil and ibrutinib were same for both the survivors and the dead at 6 months of treatment initiation.

**Conclusion A12.1:** There does not seem to be a clear relationship between average charlson age score and the outcome of the patients being dead or alive at 6 months. However, for most therapies, average charlson age score was one point higher for the dead than for those surviving. Average charlson age score did not seem to be an important risk factor in ibrutinib therapy, contrary to the chemoimmunotherapies (BR< FCFCR/PCR, Chlorambucil, and CD20 mono) therapies

***Hypothesis 12.2: Length of survival will be longer for the patients with lower charlson comorbidity index scores for CT/CIT and NA therapies.***

**Strategy A12.2:** Limit the study population to only those patients who had at least 6 months of follow-up. From this sub-cohort, create two groups of patients, one group comprising patients on ibrutinib, PI3K, and venetoclax and the second group comprising patients on the remaining six therapies. Determine OS (in days) for patients on the novel agents and CT/CIT treatments groups. Classify patients in each treatment

group into one of three CCI categories, stratified in accordance with Charlson age score, CCI 1-3 (Low), CCI 4-7 (Moderate - High) and CCI ≥ 8 (Very High). Compare the association between CCI scores and survival times in each therapy (CT/CIT and NA) and for NA vs CT/CIT, using the low CCI category as reference with student t-test.

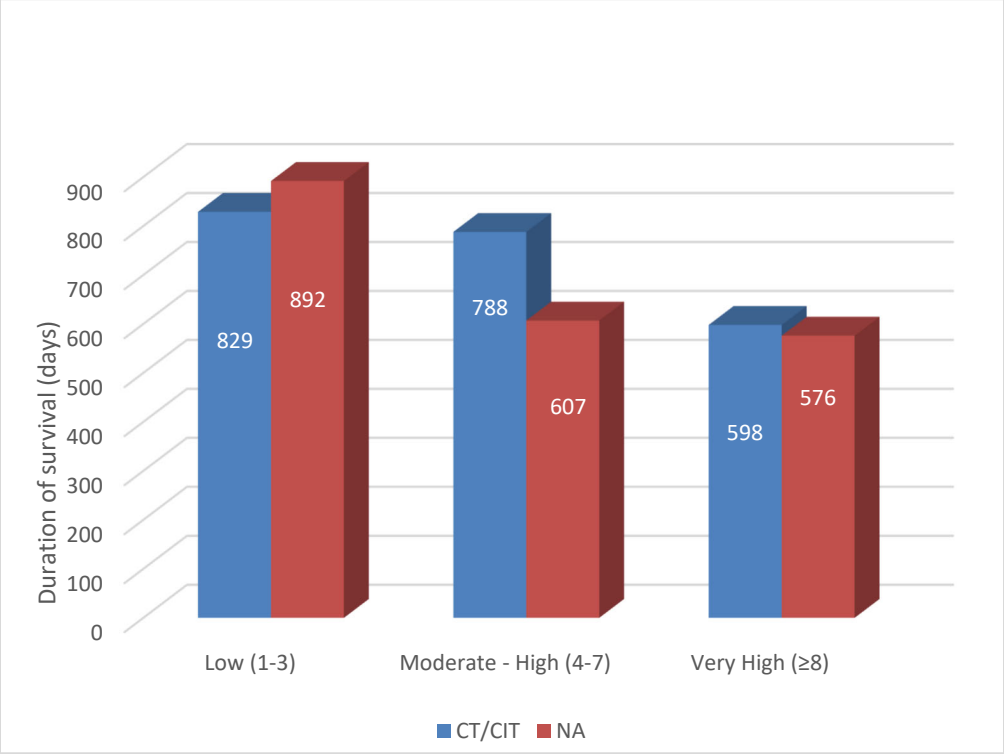



**Figure 4.26** Relationship between Charlson Age Score and Survival Times within 6 months of treatment initiation **(A12.2.)**

**Interpretation A12.2:**

- For both CT/CIT and NA, survival times tended to decrease with increasing charlson comorbidity scores.
- Within each therapy, no association was determined between the CCI score and survival time when NA patients with low CCI were compared with those with moderate – high CCI (p= 0.1978) and those with Very high CCI (p = 0.0978). Similarly, no association was determined when CT/CIT patients with low CCI scores were compared with those with moderate - high CCI score (0.6648) and those with very high CCI scores (0.1314).
- Overall, CT/CIT patients had significantly longer survival within 6 months of treatment initiation, compared to the NA patients (p = 0.031), When the two groups were compared at the level of the different CCI categories, at the low CCI score category, patients on NA had longer survival times compared to those on CT/CIT but not statistically significant (p = 0.776), while at all other levels, the CT/CIT patients had significantly longer survival, at moderate - high CCI category (p=0.0106).

**Conclusion A12.2:** No association was found between CCI scores and survival times in both NA and CT/CIT therapies, so the hypothesis of longer survival for lower CCI scores is rejected.

Though patients tended to have shorter survival times as the stratified charlson age score increased from low, moderate- high and very high score categories, none of the differences was significant.

Between NA and CT/CIT therapies, the latter had significantly longer survival with higher comorbidity index score than the NA therapies.

**Aim 13: Determine the relationship between co-medications and patient mortality at 6 months post treatment initiation.**

***Hypothesis A13.1: The proportion of patients on select co-medications that are dead at 6 months will be same for all nine therapies.***

**Strategy A13.1:** Create a sub-cohort of patients who were on co-medications. From this sub-cohort, create two groups of patients based on 6-month mortality (Dead, Alive). From the group of those that were dead, determine and compare the proportion of patients on the various co-medications for each 1L therapy.

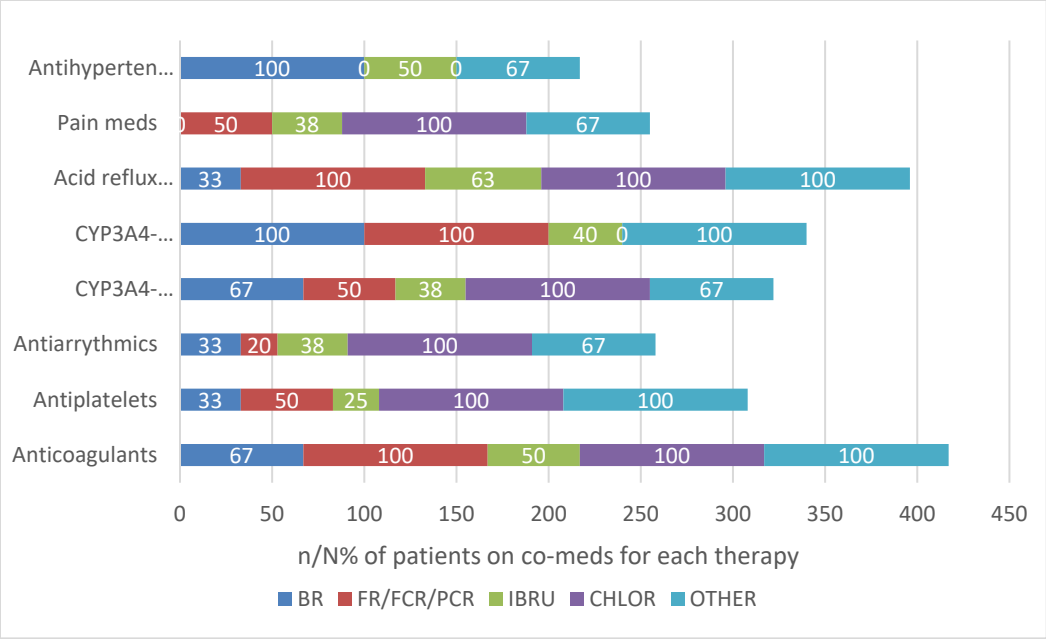



**Figure 4.27** Proportion of Patients on different co-medications that were dead at 6 months, for the Nine select therapies. **(A13.1.) (Note:** No deaths at 6 months occurred for PI3K, venetoclax, CD20 monotherapy, and chlorambucil + CD20 therapies)

| Death @ 6 months | BR | | FR/FCR/PCR | | IBRU | | PI3K | | VEN | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Dead | Alive | Dead | Alive | Dead | Alive | Dead | Alive | Dead | Alive |
| N | 3 | 164 | 2 | 85 | 8 | 160 | 0 | 4 | 0 | 2 |
| On co-meds | 3 (100%) | 151 (92%) | 2 (100%) | 80 (94%) | 7 (88%) | 138 (86%) | - | 4 | - | 2 |
| Not on co-meds | 0 | 13 (8%) | 0 | 5 (6%) | 1 (13%) | 22 (14%) | - | 0 | - | 0 |
| Range of # co-meds | 3-6 | 1-8 | 3-7 | 1-8 | 2-6 | 1-8 | - | 1-7 | - | 1 |

| Death @ 6 months | CHLOR | | CD20+CHLOR | | CD20 MONO | | OTHER | |
|---|---|---|---|---|---|---|---|---|
| | Dead | Alive | Dead | Alive | Dead | Alive | Dead | Alive |
| N | 1 | 120 | 0 | 50 | 0 | 31 | 3 | 22 |
| On co-meds | 1 (100%) | 101 (84%) | - | 46 (92%) | - | 29 (94%) | 3 (100%) | 21 (95%) |
| Not on co-meds | 0 | 19 (16%) | - | 4 (8%) | - | 2 (6%) | 0 | 1 (5%) |
| Range of # co-meds | 6 | 1-8 | - | 1-7 | - | 1-8 | 5-8 | 1-8 |

**Table: 4.9** Proportions of Patients dead or alive on the nine select therapies + concomitant medications. **(A13.1)**

**Interpretation A13.1:**

- From our study, there was no difference in the average number of co-medications for those who died and those who survived.
- Across all therapies, a greater percentage of patients were on concomitant medications (88%-100%) when compared with those not on co-medications (0-16%) for both the dead and those who survived. There were no patients on concomitant medications that were dead at 6 months for PI3K, venetoclax, CD20 monotherapy, and chlorambucil + CD20 therapies.
- For patients on ibrutinib who died within six months and who were on concomitant medications, the most prevalent concomitant medication was acid reflux medications (63%), followed by antihypertensives (50%), anticoagulants (50%), CYP3A4 inducers (40%), and CYP3A4 inhibitors (38%).
- For FC/FCR/PCR, the order was acid reflux medications, anticoagulants, and CYP3A4 inducers, each at 100%, followed by all others at 50%, except for antihypertensives at 20%.

**Conclusion A13.1:** Proportion of patients concomitantly on various co-medications who died within six months of therapy initiation was different for the different therapies. The null hypothesis of no difference is rejected.

***Hypothesis A13.2: The proportion of patients on select co-medications that are dead or alive at 6 months will be same for CT/CIT and NA therapies.***

**<u>Strategy A13.2</u>:** Create a sub-cohort of patients who were on the select co-medications. From this sub-cohort, create two groups of patients based on 6-month mortality (Dead, Alive). Determine and compare the proportion of patients on each co-medication for the CT/CIT and NA therapies.

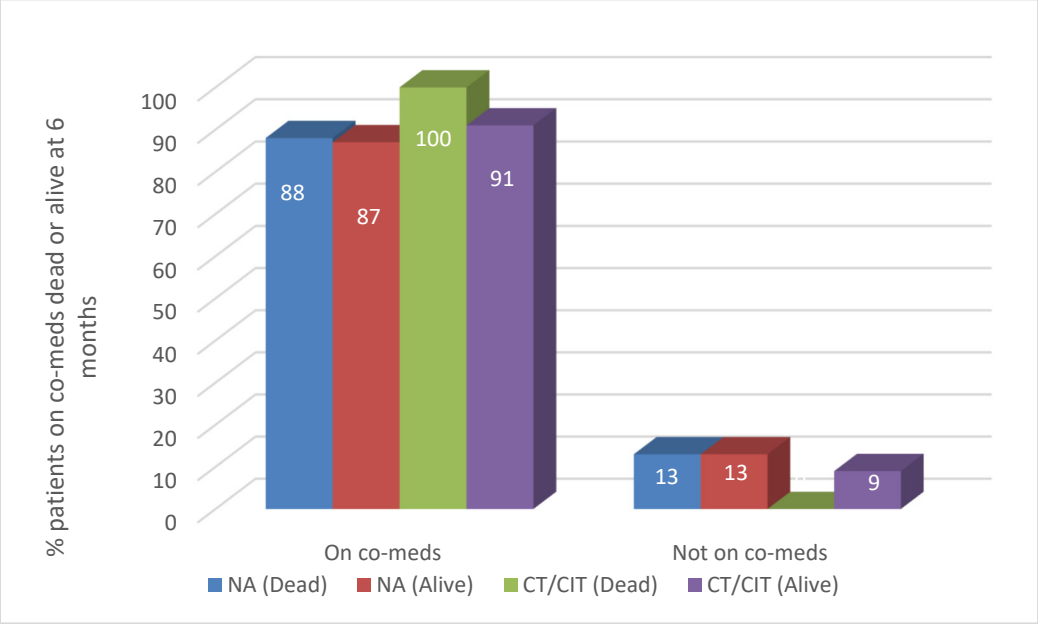



**Figure 4.28** Proportions of Patients dead or Alive at 6 months for the CT/CIT and NA**. (A13.2.)**

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| | NA (Dead) | NA (Alive) | CT/CIT (Dead) | CT/CIT (Alive) |
|---|---|---|---|---|
| On co-meds | 7/8(88%) | 144/166(87%) | 9/9(100%) | 428/472(91%) |
| Not on co-meds | 1/8(13%) | 22/166(13%) | 0/9 | 44/472(9%) |
| Range of # co-meds | 2-6 | 1-8 | 3-8 | 1-8 |

**Table 4.10** Proportions of Patients dead or alive on CT/CIT and NA therapies + concomitant medications **(**A**13.2.1.)**

**Interpretation:**

- The data shows that patients on CT/CIT therapy who were on concomitant medications and dead at 6 months (100%) were greater in proportion, when compared to those on NA (88%), though chi square analysis does not show this difference to be statistically significant (p=0.471).
- 91 % of the survivors at 6 months were on co medications in the CT/CIT therapy and 87% in the NA therapy. That means, for patients on CT/CIT and co-medications, there is a 9% difference between the dead and alive, similar difference was observed for the patients not on co-medications. This difference reduces to 1% and 0% for the NA therapies.

**Conclusion A13.2:** Alive or dead, a greater proportion of patients were on co-medications in the CT/CIT than NA therapies, rejecting the null hypothesis of no difference. Concomitant medications had a greater negative impact on mortality for CT/CIT when compared with the NA therapies.

***Hypothesis A13.3: Being on each of the select co-medications will increase the risk of death for patients in the CT/CIT, NA, FC/FCR/PCR and Ibrutinib therapies.***

**Strategy A13.3:** From the cohort, create two groups (Dead, Alive) of patients based on 6-month mortality. For each group, determine the proportion of patients on each co-medication or not on co-medication, for the CT/CIT, NA, FC/FCR/PCR and Ibrutinib. Determine the relative risk of death for patients on co-medications for each therapy.

| Co-medication | CT/CIT | NA | FC/FCR/PCR | IBRU |
|---|---|---|---|---|
| On co-meds | ∞ | 1.07 | ∞ | 1.11 |
| Anticoagulants | 16.83 | 2.48 | ∞ | 2.57 |
| Antiplatelets | 6.37 | 0.98 | 5.21 | 0.97 |
| Antiarrhythmics | 1.9 | 0.72 | 1.81 | 0.69 |
| CYP3A4 inhibitors | 4.97 | 1.33 | 2.22 | 1.34 |
| CYP3A4 inducers | 8.17 | 1.52 | ∞ | 1.51 |
| Acid reflux | 2.86 | 2.1 | ∞ | 2.07 |
| Pain | 2.56 | 0.63 | 0.53 | 0.6 |
| Anti-hypertensives | 1.74 | 0.89 | 0 | 0.89 |

**Table. 4.11** Relative Risks of Concomitant Medications on 6-months mortality for nine FC/FCR/PCR, Ibrutinib, CT/CIT and NA therapies. **(A13.3.1)**

**Interpretation A13.3:**

- Of the 655 CLL patients on 1L therapy, 94% of those who were dead at 6 months subsequent to treatment initiation were on at least one concomitant medication, compared to 90% of those who were alive at the same period.
- An analysis of the effect of concomitant medications showed an infinitely large relative risk of death in 6 months for the CT/CIT patients who are on various combinations of the select co-medications, contrary to no appreciable increased risk of death (RR 1.07) for same category of NA patients.
- For the CT/CIT therapy, the greatest risk is with anticoagulants at nearly 17 times the risk of death when compared with those not on the medication. The order of effect size of the different concomitant medications on death outcome at 6 months is anticoagulants > CYP3A4 inducers > antiplatelets > CYP3A4 inhibitors > acid reflux medications, in that order. For the NA, the effects of the anticoagulants on the risk of death (2.5 times the risk), acid reflux (2 times the risk), and CYP3A4 modulators (1.3 and 1.5 times the risk) seem to be most important.
- With the novel agents, some medications such as pain medications, antiarrhythmics, and antihypertensives had a somewhat protective effect on 6-month mortality, the risk of death for patients concomitantly on novel agents and these co-medications seem less likely.
- For patients initiated on FC/FCR/PCR and on anticoagulant, CYP3A4 inhibitors and acid reflux co-medications, the risk of death is infinitely large when compared to those not on these co-medications.
- For ibrutinib, the relative risk pattern mirrors that in the NA category.

**Conclusion A13.3:** The effect of the select concomitant medications on 6-months mortality of CLL patients on CT/CIT and NA are variable, depending on which medication is involved. Generally, risk of death increased with concomitant medication for several medications, but not for others. Therefore, we cannot generally reject or accept this hypothesis.

Relative risk of death was several times higher in CT/CIT category, compared to the NA category. Similar pattern was observed for FC/FCR/PCR and ibrutinib. Concomitant use of pain medications and antihypertensives seem to have reduced risk effect on the NA category and ibrutinib.

# CHAPTER 5

# DISCUSSION AND CONCLUSION

## DISUCSSION

Our retrospective study used data from the VHA for CLL patients with index date between 2014 -2018 to evaluate the use, trends in uptake, treatment patterns, and outcomes of select classes and categories of CLL therapies. Trends in uptake for the study years was accomplished in three lines of therapy, while further in-depth analysis of treatment patterns and outcome was conducted for the previously untreated patients on first-line CLL therapies only.

### *Specific Aim 1*

Our study described the trends in the clinical use of frontline CLL therapeutic agents, from calendar year 2014 – 2018 among adult veterans receiving treatment for CLL from the Veterans Health System. Our results show that by the year 2014, chemoimmunotherapies remained the standard frontline therapy, however, rapid decline in their use with marked increases in the utilization of novel agents were already being observed, and a rapidly transitioning treatment pattern was emerging.

Chemoimmunotherapy (FR/FCR/PCR (53%), BR (44%), and chlorambucil +CD20 (42%)) were primarily and more commonly used in previously un-treated patients, compared with their use in second line /relapsed/refractory patients (26%, 20%, and 31% respectively). The novel agents were employed more in second line

/relapsed/re-fractory treatments, compared to previously untreated patients. Ibrutinib's use was 51% in 2L, and 16% in 1L. Similar pattern was seen with the other novel agents venetoclax (37% vs 1%), P13K (37% vs 3%) (Appendix I Table 1). However, the last two, venetoclax and PI3K as well as CD20 monoclonal antibody monotherapies were most commonly used as 3L+ (third line-plus of therapy) agents.

If we examine the uptake by treatment line, we observe that chemoimmunorherapy was the most common treatment in previously untreated patients (1L) and in third-plus line of therapy, while the novel agents were most commonly used in second line for relapse patients. This is consistent with the reports of another real-world study which found that between October 2015 and February 2018, chemoimmunotherapy was more common in previously untreated patients than in relapse patients (42% vs 23%), while ibrutinib was more common in relapse patients than treatment naïve patients (51% vs 39%). It also reported that overall, 44% of the patients received ibrutinib, followed by a third of all patients who received chemoimmunotherapies.[109] In contrast, 55% of our study patients received chemoimmunotherapies overall, regardless of line of therapy, while 36% received ibrutinib. The reason for this difference between our findings and that of Mato et al could be the nature of the population and practice-setting. Their study was based on data from the 'informCLL' registry, which comprises patients from community-based practices who may have greater options and willingness to pay for the newer agent than the VA patients whose access to treatment choices are largely controlled by what the VA offers.

We also observed that overall, within the study period, anti-CD20 monotherapies (19%), BR (13%), and chlorambucil (11%), were the most common chemoimmunotherapies, regardless of line of therapy, while ibrutinib was the most common novel agent. This is different from other studies that showed BR to be more predominantly used, followed by the anti-CD20 monotherapies. Investigators evaluating treatment records for 110,000 cancer patients and over 6.7 million drug administrations available in the IntelliDose® during the years 2010-2013 found that BR was the most common regimen used, followed by rituximab monotherapy as the second most common regimen across all lines of therapy.[171] Patterns of CLL treatments have been rapidly transitioning for over a decade and half. Different studies in different practice settings/populations have reported different results in the real-world patterns of treatment among CLL patients in the United States. Our findings however are consistent with literature reports that evaluated CLL treatment trends using the SEER Patterns of Care dataset from 2008-2016 which showed that while CIT remained the standard frontline therapy, within the period studied, the use of Bendamustine / Rituximab (BR) had increased, taking over from fludarabine / cyclophosphamide / rituximab (FCR).[172] Prior the advent of novel agents, anti CD20 agents were used commonly not just as components of chemoimmunotherapies but also as monotherapies in treatment of CLL especially maintenance therapies in refractory/re-lapse patients and older patients. [41, 173-175] This may explain their predominant use in the third line of therapy in our study.

In the first line of therapy, on the aggregate, the chemoimmunotherapies (73%) dominated the treatment landscape in treatment-naïve patients in a 3:1 ratio when

compared to the novel agents (27%). However, they had a decreasing trend in uptake, from 2014 to 2018, as the novel agents' uptake was gradually on the increase. This demonstrates that the approval of novel targeted agents for first-line treatment clearly affected the first line use of chemoimmunotherapies, however, the latter still remained the preferred choice for first-line therapy at the time of our study (which included the pre- and post- approval of the first novel agent).

Ibrutinib (with or without anti-CD20 agent) at 25%, was the most used agent in the 1L of therapy in our study, closely followed by BR (25%). It is interesting to note that despite the lack of approval for its unrestricted first line use in 2014, (except in patients with del 17p mutation), the use of ibrutinib in 1L grew from 17% of CLL therapies used in 2014, 21% in 2015, 2016 (30%), 2017 (37%) and 2018 (56%), taking over from BR as the most common first line therapy by 2016, following its approval for use in previously untreated patients earlier that year (Appendix I table 2). This is consistent with other published reports that observed similar changing treatment patterns that the use of ibrutinib increased from 10.5% in 2014 to 13.6% in 2015, while the use of BR declined from 36.1% in 2011 to 31.6% in 2015 in the 1L setting.[176]

It could be explained that the use of ibrutinib in first line in 2014 and 2015 was not due to its approval for patients with del 17p mutation which came in 2016, since only about 5% of previously untreated patients have del(17p).[177]Another possible reason could be a manipulation of the system through the broad nature of FDA's approval of ibrutinib use for patients who have received 'at least one prior therapy'. It could be interpreted to

include patients who have not necessarily failed a prior therapy but tried one. Such people could very easily be placed on ibrutinib. Therefore, a patient could take a few days of a monotherapy and be switched to ibrutinib probably with a claim of a side effect. This is supported by the reports of another study that found that 10% of patients used ibrutinib in 1L prior to its 2016 approval for unrestricted first-line use. However, of this number, only 21% of the patients had 17p deletion.[178] Regardless, when it was finally approved in March 2016 for unrestricted first line use following the result of the RESONATE-2 study, our study observed a surge in usage that made it a preferred therapy in 1L. By the year 2018, ibrutinib had received over 10 approvals for various uses in CLL and this will explain its use in over 56% of the patients at the point.

Ibrutinib was predominantly used (58%) as a 2L therapy agent, it was also the most preferred (51%) of all therapies in this treatment line. Its preferential use in 2L is understandable because its first FDA approval for use in CLL was in the relapse/refractory cases. In the second line, ibrutinib dominated as the preferred therapy throughout the period studied. Its uptake increased steadily from about 51% of 2L CLL therapies in 2014, 54% in 2015 and 2016 each year, 56% in 2017, to nearly 60% in 2018. On the aggregate, in the second line uptake, almost 70% of patients were on novel agents, while 31% were on CT/CIT. When one examines the trend in uptake for the NA, there is an over 30% increase from 52% in 2014 to over 80% in 2018. This trajectory is understandable because all novel agents in our study were first approved for use in

relapse / refractory CLL. Similar to the trend in 1L, a continuous decrease in uptake of the CT/CIT (48% in 2014 – 18% in 2018) was also observed in the 2L.

The anti-CD20 monotherapy was used predominantly (78%) as a third-plus line of therapy ($3^{+}$L) agent and it was the preferred therapy (31%) in this treatment line. Here also, the proportion of patients on the CT/CIT was predominant in a 2:1 ratio when compared with the novel agents (62% versus the 34%), a result that was somewhat unexpected. This trend in uptake was fairly constant for the years 2014 – 2017. Most of the advantage for the chemoimmunotherapies was contributed by the anti-CD20 monotherapies, their combinations with chlorambucil and BR. Perhaps this domination by the CT/CIT in this line of therapy may be explained by the increasing use of the monoclonal anti-CD20 monotherapies especially rituximab and ofatumumab as maintenance therapy after chemoimmunotherapy induction. Although not yet recommended for general clinical practice, their use in this sequence has been shown to yield better progression free survival compared to than observation alone.[179,180] Also data from real world evaluation of treatment outcomes with ibrutinib show that anti-CD20 monotherapy is one of the most common therapy employed after ibrutinib discontinuation.[181] With the advent of the novel therapies into 1L use, some experts have expressed the opinion that the use of chemotherapy remains an option in third and higher lines of therapy especially in cases where patients failed first line and second line novel agents therapy, others have argued that chemoimmunotherapy has no place in refractory

CLL.[182] Our study shows that in routine clinical practice for the period studied, chemoimmunotherapies were predominantly used in 3L+ of therapies in CLL treatment.

Another observation that is worthy of note in the observed treatment patterns is the trajectory of another novel agent, venetoclax. While the first line use of venetoclax was negligible, there was a rapid increasing trend in its uptake in the 2L and $3^{+}$L lines of therapy, to the extent that it had surpassed that of ibrutinib as the most common therapy in the third and higher lines of therapy by 2018 (appendix 1, figures1 and 2). Venetoclax was approved for use in relapse CLL in 2016 and between that year and 2018, the uptake rose from 3% of all 2L CLL therapies in 2016, 9% in 2017 to 19% in 2018. Similar trend was observed in the third plus higher lines of therapy, 4% in 2016, 10% in 2017, and 27% in 2018. Two different though related reasons may explain this large growth in uptake. Venetoclax is currently FDA and EMA-approved for relapsed CLL with del17p13 while patients without del17p13/*TP53* mutation, receive the PI3K inhibitor idelalisib.[183,184] It is also considered a reasonable standard intervention in patients who fail ibrutinib therapy.[100 184] Recent data has shown that therapy with idelalisib in the relapse setting is not very effective, thus, an off-label approach that is current practice is to use venetoclax in the relapse setting even if 17p del is absent.[60,186] In addition to the fact that venetoclax has shown robust activity and good tolerability in CLL patients who have failed ibrutinib or idelalisib, it is also used in the few patients who are unable to use any of the two therapies.

Secondly, venetoclax, a BCL inhibitor has remarkable activity in CLL, especially in patients who have had substantial pretreatment.[53] It demonstrated the potential to become a definitive treatment for those who achieve a complete response because it has the ability to cause deep remission by inducing minimal residual disease negativity, unlike the BCR inhibitors which have to be given indefinitely until unacceptable toxicities or disease progression emerge.[187] Based on these, recently, venetoclax became the second targeted agent approved for first line use in CLL, in combination with a rituximab or obinutuzumab.[86,73,188] This ability of venetoclax to deliver the combined beneficial effects of chemoimmunotherapies (definite course of treatment, high MRD negativity) with the efficacy of ibrutinib (long PFS), is a potential driver of the current upsurge in its uptake. The results of our study are consistent with these principles as the potential reason for the increasing surge in the uptake of venetoclax. especially as salvage therapy in 3L+ lines because the greatest surge in uptake was observed in the third-plus of therapy.

***Demographics and Clinical Characteristics of the Patients in the 1L therapy***

The average age of 70 years obtained for our population is slightly below the 72-73 years reported for the US population but consistent with 69 – 71 years reported from the VA Health system[9,189,190]. 47% of our study population are 65 – 74 years old, 24% are under 65 years and 29% are over 74 years old. This is consistent with reports that 70% of CLL patients are over 65 years old,[9] predominantly males (99%) of white race (85%), consistent with the knowledge that CLL affects predominantly males of Caucasian race.

***Specific Aims 2 and 3***

Our study found no statistically significant difference in overall survival at six months for the nine select 1L therapies, using ibrutinib as the reference. OS was measured in terms of the percentage of patients surviving at 6 months post treatment initiation. The survival rate (Appendix 2, table 1) for patients on ibrutinib was 95%, BR (98%), FC/FCR/PCR (98%) and chlorambucil (99%). Only the group "OTHER" therapy was significantly lower in the proportion of survivors. On the aggregate, there was no significant difference in overall survival rate at 6 months between the novel agents and the chemoimmunotherapies. The Kaplan Meier curves show that survival probabilities are higher for the chemoimmunotherapies than for the novel agents (figure A3.1)

These observations are somewhat unexpected and concerning, considering literature reports of the impact of the novel agents especially ibrutinib, and venetoclax on frontline CLL therapy. Ibrutinib was approved for first line use based on the clinical trial result that demonstrated improvement in median PFS and OS in patients treated with ibrutinib (indefinite) versus chlorambucil (48 weeks). We may not be able compare our study with the finding of 98% survival rate at 24 months for ibrutinib, with a relative risk of death that was 84% lower in the ibrutinib group than in the chlorambucil group (hazard ratio, 0.16; P=0.001).[191] This is because of the limited time period (6 months) for the OS analysis in our study, which is much shorter than the 24 months for the RESONATE-2 study. Furthermore, there may be limitations of sample size and other confounders such as comorbidities, 17p del status, and disease severity (Rai staging). The RESONATE-2 study population was a more fit group with one third of the patients

having a cumulative illness rating scale score greater than 6 (suggestive of a relatively fit cohort) and Eastern Cooperative Oncology Group (ECOG) performance-status score of 2 or less (on a scale from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing disability). However, the mean CCI score in our study was 5, indicating a cohort of patients with intermediate to high severity comorbidities. Our study did not exclude patients based on genetic aberrations and disease staging while the RESONATE-2 trial excluded patients with 17p del.

***Specific Aim 4***

In our findings, targeted therapies, venetoclax, ibrutinib and PI3K had the longest time to first treatment (TTFT) among the nine select therapies. TTFT for BR, CD + Chlor and FC/FCR/PCR, were all significantly shorter than that of ibrutinib. Patients with early-stage, low risk (Binet 0) are normally not treated until disease progression according to NCCN and iwCCL guidelines. Generally, the pattern seen on the aggregate level, is that patients initiated on the novel therapies had significantly longer TTFT, longer time to initial treatment discontinuation (TIDC), and shorter time to next treatment (TTNT) when compared with those initiated on chemoimmunotherapies ($p = 0.00001$). About 30% of all newly diagnosed CLL may never go into treatment, while it takes a median of 7 years for patients with low to intermediate risk to initiate therapy, and 2 years for high or very high-risk patients.[32] Therefore, the nature and aggressiveness of the disease determines how early treatment should be initiated. It follows then that the more aggressive disease tends to go into therapy sooner. From our study, patients initiated on

chemoimmunotherapies had a shorter time to first treatment, meaning that the more aggressive diseases were initiated on chemoimmunotherapies (2.8 years) compared to the novel agents (4.3 years). The TTFT of 3.2 years observed for all patients in our study agrees with the 3.4 years reported in another real-world study.[109] It could be attributed to the fact that the CT/CIT were the preferred choice in first line therapies at the time of our study, therefore, most previously untreated patients were inadvertently initiated on them. The CT/CIT are also reported to be more effective at debulking tumors and reducing initial tumor burden, favoring their use when early intervention or sequential use is required for aggressive tumors and the possibility of eliminating minimal residual disease. The GCLLSG is currently testing this concept with a 'debulking regimen' consisting of chemoimmunotherapy (up to 2 cycles of bendamustine), followed by 6 cycles of induction therapy with targeted agent (1 to a maximum of 3 of ibrutinib, acalabrutinib, idelalisib, or venetoclax) in combination with an anti-CD20 antibody (obinutuzumab or ofatumumab), followed by MRD-guided maintenance therapy.[102] With this, results have shown that more than 90% of patients achieved MRD-negative remissions. The chemoimmunotherapies are also reported to be less tolerable due to toxicities, which could be the reason for the shorter time to treatment discontinuation. Our results observed that time to next treatment (TTNT) following treatment discontinuation for novel agents (5.5 months), is shorter when compared with approximately 15 months for the CT/CIT.

The longer time to treatment discontinuation (TIDC) for the novel agents (14 months) observed in our study compared to the CT/CIT (5 months), is consistent with

other published finding that almost 90% of patients on ibrutinib therapy in a study, did not initiate a new treatment after 2 years, indicating a longer time to treatment discontinuation.[192] The implication of these results is that the novel agents will be used for those patients who have a more indolent disease and need to stay longer in the wait-and-watch stage and have a mild or slow growing CLL, for whom aggressive treatment is not required. CT/CITs have definite treatment protocols which may have been captured as treatment discontinuation in the study, contrary to the novel agents with indefinite treatment regimen. before disease progression and next therapy and shorter duration to treatment discontinuation.

***Specific Aim 5***

Our study evaluated the use of health care resource utilization by the patients on novel agents and chemoimmunotherapies, using attendance to three facility-based care, hospital admissions, emergency room visits and urgent care visits. We found hospital admissions were slightly lower for patients on NA though not statistically different from that of the CT/CIT (p=0.0821), ER visits was significantly lower for the NA patients (p=0.0170) and no difference in urgent care visits. These findings are similar to those reported by another real-world study that ibrutinib therapy was associated with fewer days in the ER or outpatient services, fewer hospital admissions, although, these were not significantly different from that of CT/CIT.[192] The authors suggest that the higher efficacy seen with ibrutinib therapy may be the driver behind the observed lower healthcare facility utilization. However, this opinion does not account for the different

toxicity profiles for ibrutinib and CT/CIT. The CT/CIT is used more for younger fit patients because the therapy requires good renal and hepatic function to reduce the potential for its toxicities, while ibrutinib is used in patients with more diverse health status, indicating that the CT/CIT elicit more acute and toxicities that will warrant the use of hospital-based care or ER visits. The reduced healthcare facility-based care for novel agents may become important in their use due to pharmacoeconomic issues.

***Specific Aim 6***

Our study evaluated the existence of seven select clinical conditions that are considered secondary malignancies in CLL, for the nine select therapies in our cohort. We observed that overall, diffuse large B-cell lymphoma (DLBCL) at 19%, was the most prevalent complication in the cohort. DLBCL also known as Richter's Syndrome (RS) is a more aggressive B-cell lymphoma. Literature reports that between 2–8% of CLL patients will experience transformation of their disease into this complication.[193-195] It is not well understood, what risk factors promote the development of DLBCL and if such are based on the underlying biology of the disease, the duration of the disease, and treatment of the disease or the role of the CLL therapy. Our study showed that of the frontline therapies, DLBCL was most prevalent in the patients initiated on PI3K inhibitors, followed by the group "OTHER" (44%) and purine analogues- based therapy FC/FCR/PCR (36%). It was least prevalent in patients initiated on Chlorambucil (11%), chlorambucil + CD20 (14%) and ibrutinib (14%). Our result does not show any pattern

between the prevalence of DLBCL and the different therapies. This is consistent with literature reports of different prevalence rates for DLBCL for the same CLL therapy from different studies, 1.6% from the CLL4 trial and 4.1% from the CLL8 study.[81,196] It is not known whether the risk is primarily driven by the treatment itself or the same biological characteristics of CLL that determine TTFT and prognosis. It is also not known whether the risk of developing RS is treatment driven. In another study, RS appeared in nearly half of the patients before initial therapy for CLL was required. indicating that the underlying risk of developing DLBCL in CLL patients may be independent of treatment to some extent.[197] Another study showed that RS occurred prior to CLL treatment and after treatment of CLL in 46% and 54% of newly diagnosed patients, respectively, after median follow-up of 4 years.[198] Since we only obtained data on the prevalence of the select complications 6 months post therapy initiation, we are unable to make inferences on whether ourresults are treatment induced or not.

In our study, of the chemoimmunotherapies, DLBCL was seen the most in patients on FC/FCR/PCR, where it was 75% of all the complications seen in patients on this therapy. We also observed that on the aggregate, more patients on CT/CIT (20%) had DLBCL than those on NA (15%). This difference was not statistically significant, and we do not have an explanation for the observation because the possible role of the intensity of CLL therapies in the development of RS is not fully understood.[43,62, 136,196, 199-202] Exposure to combination of purine analogue-based and alkylators CLL therapies positively associated with increased risk for developing RS.[198] This was from the study of

a large cohort of newly diagnosed patients that evaluated the impact of both biological characteristics at diagnosis and treatment exposure on the risk of developing RS. There was no association found when patients were exposed to only one component of the combined therapies. Our study result tends to suggest that DLBCL is more in the more aggressive and intense treatments, because within the therapies, chlorambucil (± anti-CD20 antibodies), Ibrutinib, had the lowest prevalence of DLBCL, while the PI3K and FCR/PCR had the highest.

A comparative analysis of the prevalence of DLBCL in patients on ibrutinib compared to those on FC/FCR/PCR shows significantly (p= 0.0005) that fewer patients on ibrutinib (14%) experienced this complication vs 36% for FC/FCR/PCR. Our finding is consistent with studies that show ibrutinib to be a promising target drug for the treatment of DLBCL. In a case series of four ibrutinib-naïve patients with DLBCL, ibrutinib resulted in one complete response and two partial responses, within a median duration of six months therapy.[203] Other responses varying between 15% - 90% in clinical trials have also been reported.[204,205]

***Specific Aim 7***

Comparing the aggregated (2014 – 2017) use of CT/CIT and NA for black and white patients, our study observed a significant relationship with race. The use of the traditional chemotherapy/chemoimmunotherapy (CT/CIT) tended to be more common among the black patients than the whites (p = 0.0125), while the novel agents use was more likely in whites (p = 0.0125). Also, on yearly basis, the black patients lagged behind

the whites in uptake of the novel agents, while the CT/CIT therapies use was higher in blacks than whites. This observation is somewhat concerning because the choice of CLL therapy for a patient is guided by factors such as age, disease staging, comorbidities, presence /absence and type of genetic aberration, and frailty, not race and ethnicity. Literature reports that although the VHA is committed to equal health care quality and access to all veterans, racial disparity has persisted across a wide range of clinical areas and services, with some veterans in ethnic/minority groups still have reduced services and poorer health outcome. The black veterans were the group mainly affected in the mortality disparity for several clinical conditions.[206] Another study in the VHA showed that the 3-year mortality of colon cancer was higher in blacks than white veterans (3-y OR = 1.28 (95% CI = 1.04. 1.56)). After adjusting for age, gender, marital status charlson comorbidity score, history of cancer, and year of diagnosis, they found that the disparity was attributable to within- hospital differences.[207] Such disparity has been reported to be most prevalent in areas involving medication adherence, quantity and quality of provider communication, shared decision making and patient participation and that minorities in VHA are receiving fewer and lower quality services despite their greater need.[208] Cancer management is one clinical condition where such disparity has been identified in the VHA and one that incorporates all the potential sources of disparity listed above. The implication of this for clinical practice may be significant in mortality because patients may receive treatments that are less than optimal for their disease, with attendant poorer outcome. Other authors have also reported that poverty, race and age were notable drivers in the selection of treatments in their population of CLL patients, in their study using

Medicare data.[209] Similar variations in patterns in practice was also reported in the management of non-Hodgkin lymphoma.[210] It has been suggested that uncertainty in relative effects of new treatment, age, race and poverty-related issues create imbalances in the uptake and assimilation of new technology.[211, 212] This could be plausible reason for the observed disparity.

However, from our studies we are unable to ascertain with firm conclusions that our result reveals a racial / ethnic disparity because we are unable to determine the cause of the observed differences. The Institute of Medicine defines disparities as "racial or ethnic differences in the quality of health care that are not caused by access-related factors or clinical needs, preferences, and appropriateness of intervention."[213]

***Specific Aim 8***

The chemoimmunotherapies such as FCR have been employed in the treatment of patients who were 'fit' enough to withstand the toxicities. Typically, this excluded the frail, elderly and patients with moderate to severe comorbidities. For the latter group of patients, chlorambucil + immunotherapy was traditionally used until the advent of the targeted therapies. Recently other therapies such as ibrutinib monotherapy, venetoclax + Obinutuzumab have shown better outcomes in the elderly, the frail and persons with comorbidities. Our study observed the chemoimmunotherapies were predominantly used in the youngest age group (26%), while the targeted therapies were used most in the oldest age group (33%). This finding is consistent with reports from Mato et al 2020, that chemoimmunotherapies were predominantly used in the patients younger than 65 years

(42%), while ibrutinib was used more than chemoimmunotherapies for patients older than 65 years (55%). Our numbers however, differ from theirs. Several studies have shown that the chemomimmuotherapies have excessive toxicities that make them unsuitable for older patients who are known to also have more comorbid health conditions even though the former gives deeper remission. A retrospective analysis of 949 CLL patients which compared different CT/CIT therapies in persons older than 70 years and those younger than 70 years, found that only a very small portion of the older patients were able to tolerate the chemoimmunotherapies and receive effective treatments.[214] The targeted therapy ibrutinib has received approval expanding its use for all CLL indications, irrespective of age, genetic mutations status and performance status. It has remained the preferred first line therapy approved for use in all patients except for patients younger than 65 years with mutated IGHV. It follows therefore that the novel agents will be the treatment of choice for most elderly persons who are frail and possess many comorbidities and may not be able to tolerate the chemoimmunotherapies well. Our finding seems to be consistent with this principle.

***Specific Aims 9 and 10***

Our study cohort comprised patients 18 years – 90 years, subdivided in three age groups of <65 years, 65 -74 years and < 74 years.

The clinical situation which remains largely undecided is the use of FCR *versus* ibrutinib in young patients, especially those with mutated IgHV. Studies have shown no difference in PFS, in the use of either therapy in these patients.[215] Current version of NCCN

guidelines still recommend the use of FCR for fit younger patients, since it has been shown to give better outcome by producing longer PFS with lower MRD negativity.[216] Generally, in the United States of America, fit patients are defined as those younger than 65 years of age with a good performance status. In Europe, an additional criteria of creatinine clearance greater or equal to 70ml/min or a comorbidity rating scale score of 6 or less is required. Such patients are thought to be good candidates for FCR therapies as a front-line treatment because a close to 95% response rate and complete response of 40% - 75% have been associated with this therapy in this population.[43,47] Following the result of the ECOG-E1912 study that demonstrated longer PFS ibrutinib + rituximab in treatment naïve CLL patients younger than 70 years, when compared with FCR, and the subsequent FDA approval, NCCN guidelines currently recommends the use of either therapy in younger fit patients, the choice of which treatment should be shared decision with regards to toxicity profile of the agents, IGHV status of the patient and convenience of therapy (whether to take chronic ibrutinib therapy or have a "one and done" approach with a course of FCR).[90, 215] The data from our study found that FC/FCR/PCR compared to ibrutinib was significantly used more in the age group <65 years old ($p<0.00001$), and this predominance existed for every year studied. The reason for this observation could be that most patients prefer the option of a possible cure with FCR, based on its ability to produce low MRD negativity with the shorter (definite) course regimen compared to ibrutinib, which on the other hand, produces longer PFS with chronic use. Studies have shown that most patients prefer treatments that promise longer PFS, even if that means enduring significant adverse effects.[113] It could also be that our study predates the

approval of ibrutinib use in this population, however, this is unlikely reason because the dominance of FC/FCR/PCR in this young population was maintained beyond the approval years of ibrutinib use in the population. This finding shows that FCR is still a frontline therapy in the youngest population, the introduction of ibrutinib did not negatively impact the choice of this therapy in this age-group because the uptake of FCR remained significant lead over ibrutinib for each year studied.

On the other hand, ibrutinib was significantly ($p=0.0011$) used more in the age-group of patients older than 74 years. In patients 65 – 74 years old, there was similarity in uptake of both therapies, although ibrutinib was slightly but not significantly more.

When we evaluated the distribution of both therapies in black and white patients in all age groups to determine if race was an impacting factor. The data showed that black patients younger 75 years, were significantly less likely to receive ibrutinib while predominantly receiving FC/FCR/PCR more than their white counter parts in the youngest age group (<65 years), regardless of the fact that whites were the predominant patients in each age group.

However, in patients older than 74 years, black patients predominantly received ibrutinib compared to the whites. The reason could be that the clinical presentation of the disease in the black patients indicated a more frailty, which influenced the choice of ibrutinib over FC/FCR/PCR. Literature reports that there are racial differences in CLL patterns of presentation and outcomes. A report on CLL/SLL study

using 13 SEER registries, suggests that African Americans in the United States present with more advanced-stage CLL disease.[217]

This is corroborated by a more recent study which showed that African Americans with CLL presented more with CLL clinical characteristics associated with worse outcomes, for example, lower median hemoglobin levels, higher beta2-microglobulin (b2-m) levels, higher prevalence of unmutated IGHV gene (65% versus 47%), ZAP70 expression (58% versus 32%), and chromosome 17p or 11q deletion (28% versus 17%).[218]

Our study is the first and only study to evaluate the use of FCR and ibrutinib therapies in different age-groups and different races/ethnicities in the real-world settings, therefore, were unable to find comparator studies for our findings. However, the finding that FCR was used predominantly in the younger patients when compared to older ones, shows a compliance with the recommendations of NCCN treatment guidelines.

***Specific Aim 11***

On the aggregate, the use of CT/CIT was significantly higher than NA use in each VA priority group. Uptake of most therapies was similar across all VA priority groups, using group 1 as reference, but BR and chlorambucil were significantly used more in group 1, compared to group7-8. While there was no notable difference in the use of all nine select therapies between VA group 1 vs group 2-6, certain differences existed between group 1 vs group 7-8. BR and chlorambucil are the top two chemoimmunotherapies used in the cohort. They are not as effective as the novel agent

ibrutinib however, the latter will have a higher out of pocket cost. The use of BR and chlorambucil is lowest and the use of ibrutinib is highest in the VA priority group 7-8, compared to the other groups. This trend seems to correspond with access to VA healthcare benefits and the affordability of heath care in the groups. The priority group assignation affects how soon veterans are signed up for healthcare benefits and what they pay towards their cost of care. Group 1 receives free healthcare and no co-pays while groups 7-8 are high income veterans or those residing in high income zip codes, while groups 2-6 are a mixed-bag of veterans between the two. VA Groups 7-8 is made up of those veterans whose income though is below the geographically adjusted income for where they live, they agree to pay co-pays (group 7) as well as high income earners, living in areas whose adjusted income is above VA income limits who also agree to pay co-pays (group 8). These groups are expected to pay full co-pay for outpatient and in-patient care, as different from the other groups. It is expected that cost will not be a limiting issue in their uptake of better/more expensive health care due to higher ability to pay for care. The higher or more enhanced a priority group is, the sooner the members are signed up for immediate care and the more VA benefits accrues towards paying for members cost of care. Veterans who have service-connected disabilities are assigned to the highest priority group in the VA, while those who do not have service-related disabilities that qualify them for monthly disability compensation, and earn a higher income are assigned to the lowest. VA priority groups 1-3 receive some healthcare benefits for individuals who have service-connected disabilities, discharged due to disabling injury acquired on active duty or have received some awards for valor.

Assignation to the groups 1-3 is not based on income, financial -status or zip code. For groups 4-6, there are some income-based and financial status criteria built into their eligibility, while groups 7-8 are income and financial status driven. It may mean that priority group 7-8 members are able to pay for the more expensive and efficacious novel agents. In support of this may be the data that shows the population of CLL patients accessing care from the VA in our study, to be lowest in the priority group 7-8. This could mean that these veterans are able to afford other health insurance coverage and thus access care from other facilities outside the VA.

***Specific Aim 12***

Average charlson age score in our study population was 5, which would be considered an intermediate disease severity score. Conflicting information and data exist concerning the impact of comorbid health conditions in predicting the prognosis of CLL disease and treatment outcomes, especially in the 1L setting. Some researchers have presented data showing no association between measures of comorbidity (such as CIRS and CCI scores) and event free survival while others report significant predictive ability of comorbidities on OS and PFS.[129,219-223] Our study found that the presence of comorbid conditions did not significantly affect overall survival (survival time) because CCI score did not have an association with survival time, either in the novel agents or the chemoimmunotherapies as shown in FigureA12.2 and Appendix III, table 2. This suggests that the presence of the charlson comorbidities was not a major determinant in survival but rather the CLL disease. Comorbidities are important determinants in the

selection of treatment protocol, due to their impact on organ function, performance status and "fitness", and therefore, the ability for a given patient to tolerate aggressive therapy.[224,32,225] However, they do not feature as major considerations in determining disease severity, which in turn impacts prognosis. Our findings tend to align with these principles and are consistent with other published reports that cumulative presence of four major comorbidities (ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease and second primary malignancy) in CLL patients did not have a statistically significant impact on overall survival in a multivariate analysis, while age ($p = 0.0001$), Rai risk ($p<0.0001$) and year of diagnosis ($p<0.0001$) were significant predictors of OS.[147] In elderly patients ≥65 years, regardless of the significant difference between the median CIRS-G score of 7 for patients who had more comorbidities, versus those who had 4, no association with survival was found.[226] Another study also observed no difference in overall survival based on the number of comorbidities present ($p =0.67$).[129] Our observation is also consistent with the report that No association was found between CCI and overall CLL-related or unrelated death, however, 5-year overall survival decreased with increasing CCI score, but this trend had no effect on statistically significant effect on mortality. [232]

We also observed that overall, patients with comorbidities initiated on the chemoimmunotherapies had significantly higher OS when compared with their counterparts on targeted therapies ($p = 0.031$). Other studies have suggested that there is a relationship between high morbidity index score and poorer treatment outcome with ibrutinib therapy. In a multicenter cohort study of patients treated with ibrutinib, high

morbidity index score correlated with inferior event free survival and overall survival in both 1L and R/R settings.[227]

***Specific Aim 13***

At baseline, patients took a median of 3 medications at least six months into their index date. Reports of existing studies on the potential drug interactions in patients receiving TKIs show that acid suppressants including proton pump inhibitors, histamine 2 receptor antagonists and antacids was the most frequently implicated pharmacologic class interacting with TKIs.[228] Also, literature reports that a higher percentage of TKI-proton pump inhibitor users died when compared with those not on that combination.[229] Also, 100% of those on the FR/FCR/PCR therapy who died within the six months period following treatment initiation, were on acid reflux medications. In our study, the highest odds for death on the aggregate was seen with the anticoagulants, followed closely by the acid suppressants.

Contrary to the increased risk of death with concomitant medications seen at the 6-month period, the relative risk of a death outcome for patients on concomitant medications decreased when measured at the end of study, a trend that is similar in both the CT/CIT and the NA therapies. This may be indicative that the effect of concomitant medications in the all-cause death was smaller at this level because other long-term mortality risk factors may be in play at this time.

More importantly, the somewhat protective effect seen with antiarrhythmics and antihypertensives for the NA was lost while that of pain medications subsisted. This occurrence was demonstrated more clearly in the ibrutinib therapy. It seems that the presence of the antihypertensives and antiarrhythmic agents initially prevented the development of these CV adverse effects of ibrutinib in the first few months following ibrutinib initiation, but subsequently was overcome by the worsening of these conditions overtime, as precipitated by the novel agent. It is known that potential cardiovascular toxicities of ibrutinib include cardiac arrythmias and atrial fibrillation.[230] Real world studies of ibrutinib also reveal that hypertension of any grade is much higher in patients than the 5% reported in clinical trials. A retrospective study of 562 adult patients with lymphoid malignancies treated with ibrutinib showed that 78.3% of patients developed new or worsening hypertension. Of the 38.2% patients without a baseline hypertension, 71.6% developed new hypertension while on ibrutinib in 4.2 months. O the 61.7% of patients who had hypertension, there was worsening in 82.4%. The study also found that cases of new or worsening hypertension occurs early within 4 months, with a full manifestation of effects at over 30 months.[231]

The clinical significance of this polypharmacy may be seen in the higher relative risk of death for those on the concomitant medications.

**IMPLICATIONS FOR CLINICAL PRACTICE**

The use of chemoimmunotherapies (CT/CIT) such as BR, FCR regimens were a standard of care in CLL management, especially in previously untreated patients. Until

recently, their use remained common place in real-world clinical settings, but was fast declining over the years studied.

The CT/CIT were predominantly used in 1L and $3^{+}$L of therapies, the novel agents (targeted therapies) were predominant in the 2L.

As at the time of our study, ibrutinib was the only single-agent targeted therapy approved for CLL in the front-line setting regardless of TP53 mutation. It fast took over from the chemoimmunotherapies as the preferred therapy in both first and $2^{nd}$ lines of therapy.

The purine analogue-based therapy FCR was still predominantly used in the youngest population of CLL patients (<65 years), while ibrutinib was preferred therapy in patients older that 74 years. Both therapies were equally used in the CLL patients between 65 and 74 years

Disparities were observed between the African-American and Caucasian patients in the use of the novel agents. Black patients lagged behind in the uptake and use, compared to their white counterparts.

Between FCR and ibrutinib use, black patients were more likely to receive FCR in the patients younger than 74 years old, while white patients were more likely to receive ibrutinib. It needs to be determined if this racial disparity is driven by biology and clinical presentation of the CLL in both races.

Use of novel agents resulted in significantly fewer emergency room visits and tendency towards fewer hospital admissions, compared to the chemoimmunotherapies. The pharmacoeconomic impact of the novel agents may be weighed against the potential

cost savings from lower health care facility utilization when compared with the chemoimmunotherapies.

The novel agents were significantly associated with longer TTFT and longer TIDC with shorter TTNT, indicating that patients on these therapies took longer to commence treatment and they stayed longer on treatment but relapsed faster after treatment discontinuation. This observation becomes important in the choice of therapy for patients initiating treatment from the 'wait-and-watch' stage. The decision of which approach to treatment will be between; longer time to first treatment, with chronic medication use and shorter time to next treatment if discontinuation happens or earlier start to treatment with a 'one-and-done' treatment course and longer time to next treatment.

Diffuse large B-Cell lymphoma was the predominant complication in patients on all select therapies in our study, and generally, no significant difference was observed in its prevalence between chemoimmunotherapies and targeted therapies. However, DLBCL was significantly lower in patients on ibrutinib compared to those on FC/FCR/PCR. This observation may become important in the choice of therapy for those patients (such as those of IGHV mutated status) who are at risk of developing Ritcher Syndrome.

We did not observe any clear relationship between the average CCI score and death outcome for both the chemoimmunotherapies and novel agents., however, length of survival tended to increase with decreasing comorbidity severity. This was more evident in the chemoimmunotherapies. Therefore, for patients where comorbidity is a serious consideration in the choice of therapy, novel agents may be preferred.

Co-medications being taken at the time of treatment initiation was important in death outcome at 6 months for both the CT/CIT and novel agents at aggregate and individual levels. The type and not number co-medications was associated with relative risk of death. The risk of death while on co-medications generally is higher with the chemoimmunotherapies, however, different medications pose different levels of risk for the individual therapies. Anticoagulants, acid reflux medications, CYP3A4 inducers and antiplatelets present a high level of risk in FC/FCR/PCR therapy, while anticoagulants, acid reflux medications and CYP3A4 inducers are important for ibrutinib. Certain medications such as antihypertensives were also shown to lower the risk of death especially in ibrutinib therapy. Considering the increased risk levels, it becomes important to conduct a careful assessment of patients on acid reflux meds, anti platelets, anticoagulants and CYP modulators, in the choice of therapy for CLL management.

**CONCLUSIONS**

The targeted therapies especially ibrutinib has become standard of care in CLL treatment at the expense of the chemoimmunotherapies. However, the latter still has use in a sub-population of young CLL patients and in higher lines of therapy. The treatment pattern observed during our study period seem to be consistent with NCCN guidelines as well as the rapidly changing CLL treatment landscape and practices. Some principles that guide current practices and treatment guidelines are supported by evidence from our findings, however, other findings indicate that certain practice experiences are not. For example, treatment decisions observed from our study that FCR is more commonly used

in younger patients are in compliance with guidelines, but the use of BR over FCR may be more of practice-informed rather than guideline driven because FCR demonstrated a better PFS than BR in clinical trials.

Selection bias still exist in real-world treatment of CLL, despite the existence of treatment guidelines. Driving factors could be physicians clinical judgement of who will benefit more from certain treatment, readiness and willingness to adopt new technologies and treatment innovations.

The effect of pharmacotherapy - related issues such as drug-drug interactions from concomitant use of medications on outcomes of CLL treatment, appear to be more important in CLL-management than currently known. More research in this area is warranted.

## STRENGTHS AND LIMITATIONS

### *Strengths*

Our findings are based on real-world clinical data obtained from a patient population that would likely be encountered during routine clinical practice contrary to the selected, streamlined and more strictly controlled clinical trials patients. Our observations therefore will reflect true events and outcomes associated with CLL disease and its management.

Our study is unique in that it looked at a wide range of treatment outcomes in the management of CLL with different classes of agents in the same population. This will

more likely yield more reliable inferences based on true observations, than when different outcomes are evaluated in different populations and pieced together.

Furthermore, our study period captured a baseline period and rapidly transforming period in CLL management, our observations captured changes in real-time as they were occurring.

The study used patients' data from the largest integrated health care system in the United States, with a presence in all 50 states, therefore, the study results will be generalizable to all veteran hospitals and clinics in the United States. The data used are comprehensive, because VHA maintains repositories that include data from both hospital and clinic settings.

Furthermore, the VHA system maintains a vital status file that enables investigators to determine patient mortality, even when it occurs outside the clinic or hospital settings.

***Limitations***

Our first limitation in this study is the use of electronic medical record which does not contain all information such as relevant prognostic factors, disease staging, molecular and genetic aberrations (e.g., presence of Del(17p)/TP53 mutation), and other markers of disease severity, which could have influenced treatment choice or survival outcomes. Therefore, we are not able to evaluate the effect of all cofounders.

Secondly, some of the novel therapies regulatory approval were within the study period, therefore, only a subset of CLL patients commenced treatment within the study

enrolment period, limiting the sample size for analyses for some of the therapies. Ibrutinib obtained six approvals for use in CLL during this time period and thus we were working in a rapidly changing system.

The Veterans Health Administration system database is made up of predominantly elderly, white, male population, which constitutes our study population thus, our findings may not be generalizable to non-VHA settings.

Finally, there may be variation in the extent of physician reporting of patients' comorbidities and adverse effects. In the myriad of combinations of agents used in CLL treatment, some of the combinations might be missed, but these are not likely to be frontline therapies.

The use of electronic health records for research purposes is still evolving, and because some of these EHR systems are not created primarily for the purpose of research, but rather for patient care, they may contain errors, and there is limit to how much information that can be extracted from these.

# APPENDICES

## APPENDIX A

### Table 1. PATIENTS BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

| Baseline characteristic | All |
|---|---|
| N | 655 |
| Age (years) | N=655, 70 (33-90) |
| Age groups | -- |
| Missing | N=0 |
| 1=<65 years | 159/655=24% |
| 2=65-74 years | 307/655=47% |
| 3=>74 years | 189/655=29% |
| Male | 647/655=99% |
| Race | |
| Missing | N=8 |
| 1=White | 548/647=85% |
| 2=Black | 92/647=14% |
| 3+=Other | 7/647=1% |
| Charlson score | N=655, 2 (0-6) |
| Charlson Age score | N=655, 5 (1-10) |
| Charlson comorbidities | -- |
| Congestive heart failure | 67/655=10% |
| COPD | 144/655=22% |
| Cerebrovascular disease | 50/655=8% |
| Dementia | 7/655=1% |
| Diabetes (no complications) | 218/655=33% |
| Diabetes (with complications) | 67/655=10% |
| Hemi/paraplegia | 3/655=0% |
| HIV/AIDS | 1/655=0% |
| Liver (mild) | 42/655=6% |
| Liver (mod/severe; cirrhosis) | 4/655=1% |
| Cancer | 651/655=99% |
| Metastatic cancer | 34/655=5% |
| Myocardial infarction | 18/655=3% |
| Peptic ulcer disease | 5/655=1% |
| Peripheral vascular disease | 51/655=8% |
| Renal disease | 85/655=13% |
| Additional comorbidities | -- |
| Coronary artery disease | 82/655=13% |
| Atrial fibrillation | 70/655=11% |
| Arrhythmia | 86/655=13% |
| Deep vein thrombosis | 16/655=2% |
| Pulmonary embolism | 23/655=4% |
| Prior bleed | 45/655=7% |
| Lung diseases | 28/655=4% |
| Intestinal disorders | 27/655=4% |
| Crohn's | 0/655=0% |
| GI ulcers | 0/655=0% |

| | |
|---|---|
| High uric acid or gout | 41/655=6% |
| High cholesterol | 43/655=7% |
| Hypertension | 154/655=24% |
| Rheumatoid arthritis | 10/655=2% |
| Agent Orange exposure | 58/655=9% |
| VA Priority Group | -- |
| Missing | N=0 |
| Group 1 | 258/655=39% |
| Groups 2-6 | 279/655=43% |
| Groups 7-8 | 118/655=18% |
| Concomitant medications | -- |
| Anticoagulants | 205/655=31% |
| Antiplatelets | 159/655=24% |
| Antiarrhythmics | 270/655=41% |
| CYP3A4 inhibitors | 192/655=29% |
| CYP3A4 inducers | 307/655=47% |
| Acid reflux | 275/655=42% |
| Pain | 363/655=55% |
| Anti-hypertensives | 349/655=53% |
| Geographic region | -- |
| VISN1 | 36/655=5% |
| VISN2 | 32/655=5% |
| VISN4 | 27/655=4% |
| VISN5 | 24/655=4% |
| VISN6 | 36/655=5% |
| VISN7 | 32/655=5% |
| VISN8 | 52/655=8% |
| VISN9 | 32/655=5% |
| VISN10 | 38/655=6% |
| VISN12 | 40/655=6% |
| VISN15 | 34/655=5% |
| VISN16 | 43/655=7% |
| VISN17 | 18/655=3% |
| VISN19 | 39/655=6% |
| VISN20 | 31/655=5% |
| VISN21 | 34/655=5% |
| VISN22 | 55/655=8% |
| VISN23 | 52/655=8% |
| Laboratory values | -- |
| White blood cell count | N=598, 59 (1-564) |
| Platelets | N=584, 142 (0-468) |

Table A2. Outcome Variables for all therapies combined.

| Treatment outcome | All |
|---|---|
| Timed outcomes, n, median (range), days | -- |
| TTFT=Time from dx to initiation | N=639, 1164 (0-5793) |
| TIDC=Time from initiation to dc | N=655, 212 (0-1644) |
| TIFU=Time from initiation to eofu | N=655, 961 (0-1780) |
| TTNT=Time from dc to next tx | N=563, 295 (1-1509) |
| OS1=Initiation to death | N=217, 740 (9-1833) |
| OS2=Dc to death | N=217, 544 (1-1748) |
| Outcomes (in 6 months), n/N=% | -- |
| Emergency room visits | 257/655=39% |
| Urgent care visits | 24/655=4% |
| Hospital admissions | 200/655=31% |
| Death | 17/655=3% |
| Outcomes (overall), n/N=% | -- |
| Emergency room visits | 464/655=71% |
| Urgent care visits | 69/655=11% |
| Hospital admissions | 434/655=66% |
| Death | 217/655=33% |
| Complications, n/N=% | -- |
| Diffuse large B-cell lymphoma | 124/655=19% |
| Hodgkin’s lymphoma | 22/655=3% |
| Stem cell transplant | 13/655=2% |
| Skin cancer | 21/655=3% |
| Lung cancer | 21/655=3% |
| Bladder cancer | 16/655=2% |
| Prostate cancer | 58/655=9% |

## APPENDIX B

**Table B1:** Distribution of the Nine Select treatments across the Three lines of Therapies

| Treatment | 1L | 2L | 3+L | All Lines |
|---|---|---|---|---|
| BR | 167/379 (44%) | 77/379 (20%) | 135/379 (36%) | 379 |
| FR/FCR/PCR | 87/165 (53%) | 43/165 (26%) | 35/165 (21%) | 165 |
| Ibrutinib (+/- CD20) | 168/1077 (16%) | 552/1077 (51%) | 357/1077 (33%) | 1077 |
| PI3K inhibitor (+/- CD20) | 4/125 (3%) | 46/125 (37%) | 75/125 (60%) | 125 |
| Venetoclax (+/- CD20) | 2/154 (1%) | 57/154 (37%) | 95/154 (62%) | 154 |
| Chlorambucil (- CD20) | 121/337 (36%) | 41/337 (12%) | 175/337 (52%) | 337 |
| CD20 + Chlorambucil | 50/120 (42%) | 37/120 (31%) | 33/120 (28%) | 120 |
| CD20 Mono | 31/553 (6%) | 88/553 (16%) | 434/553 78% | 553 |
| Other | 25/70 (36%) | 12/70 (17%) | 33/70 (47%) | 70 |
| CT/CIT | 330/1320 (25%) | 298/1320 (23%) | 845/1320 (64%) | 1320 |
| NA | | | 527/1356 (39%) | 1356 |

**Table B2.** Yearly Uptake of Nine Select First-line CLL therapies 2014 -2018

| Treatment | 2014 | 2015 | 2016 | 2017 | 2018 | Total |
|---|---|---|---|---|---|---|
| BR | 67 | 54 | 26 | 15 | 5 | 167 |
| FR/FCR/PCR | 38 | 24 | 12 | 12 | 1 | 87 |
| Ibrutinib (+/- CD20) | 37 | 39 | 37 | 35 | 20 | 168 |
| PI3K inhibitor (+/- CD20) | 0 | 3 | 1 | 0 | 0 | 4 |
| Venetoclax (+/- CD20) | 0 | 0 | 1 | 1 | 0 | 2 |
| Chlorambucil (- CD20) | 36 | 37 | 24 | 17 | 7 | 121 |
| CD20 + Chlorambucil | 13 | 19 | 12 | 4 | 2 | 50 |
| CD20 mono | 15 | 7 | 4 | 5 | 0 | 31 |
| Other | 6 | 5 | 8 | 5 | 1 | 25 |
| All novel therapies | 37 | 42 | 39 | 36 | 20 | 174 |
| CT/CIT | 175 | 146 | 86 | 58 | 16 | 481 |

**Table B3.** Distribution of novel treatments and CT/CIT within the lines of therapy

| Therapy | 1L (N=655) | 2L (N=953) | $3^{+}$L (N=1372) |
|---|---|---|---|
| NA | 174 (27%) | 655 (69%) | 527 (34%) |
| CT/CIT | 481 (73%) | 298 (31%) | 845 (62%) |

**Figure B1**. Yearly Uptake of Nine Select 1L CLL therapies 2014 -2018

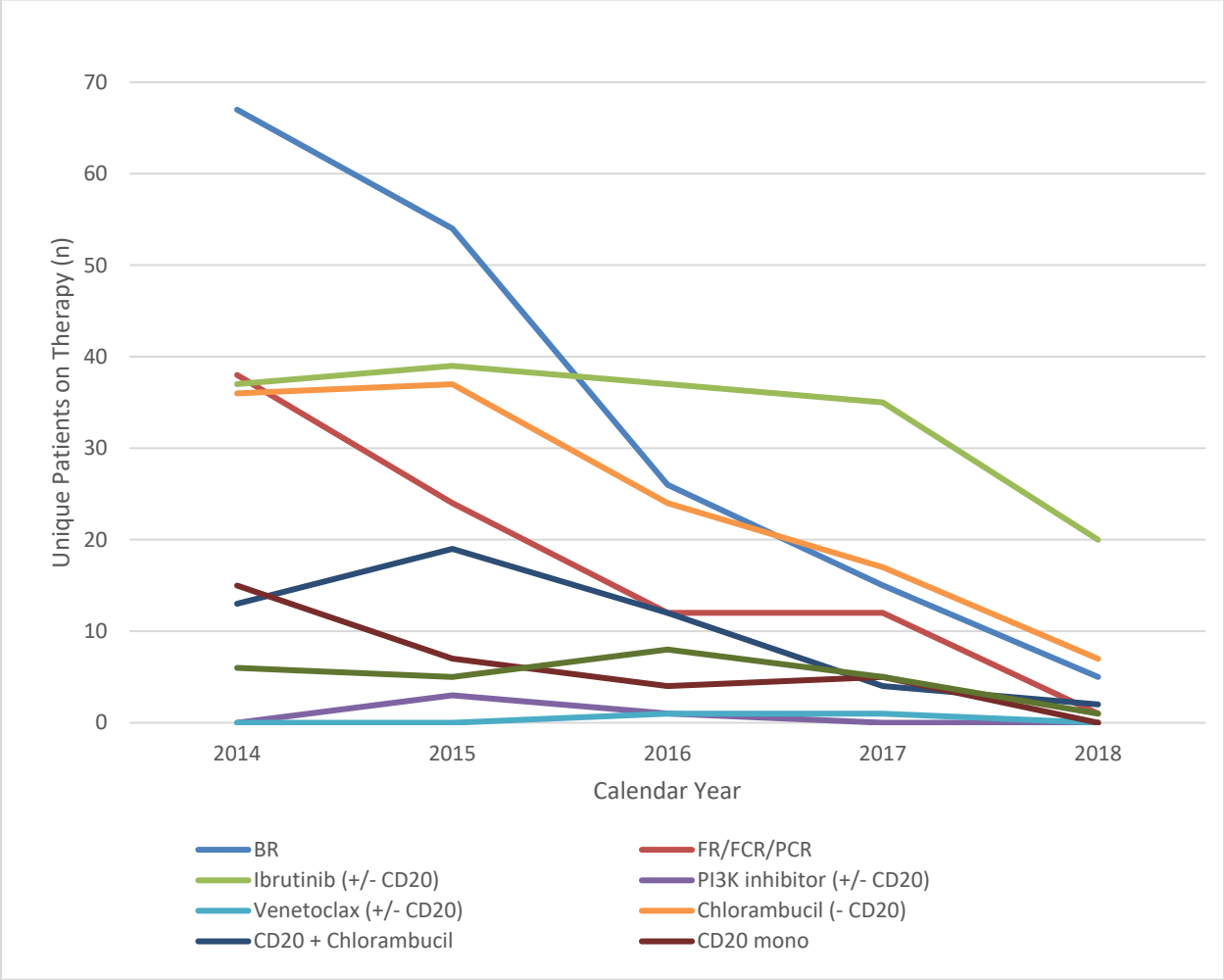


**Figure B2.** Yearly Uptake of Nine Select 2L CLL therapies 2014 -2018

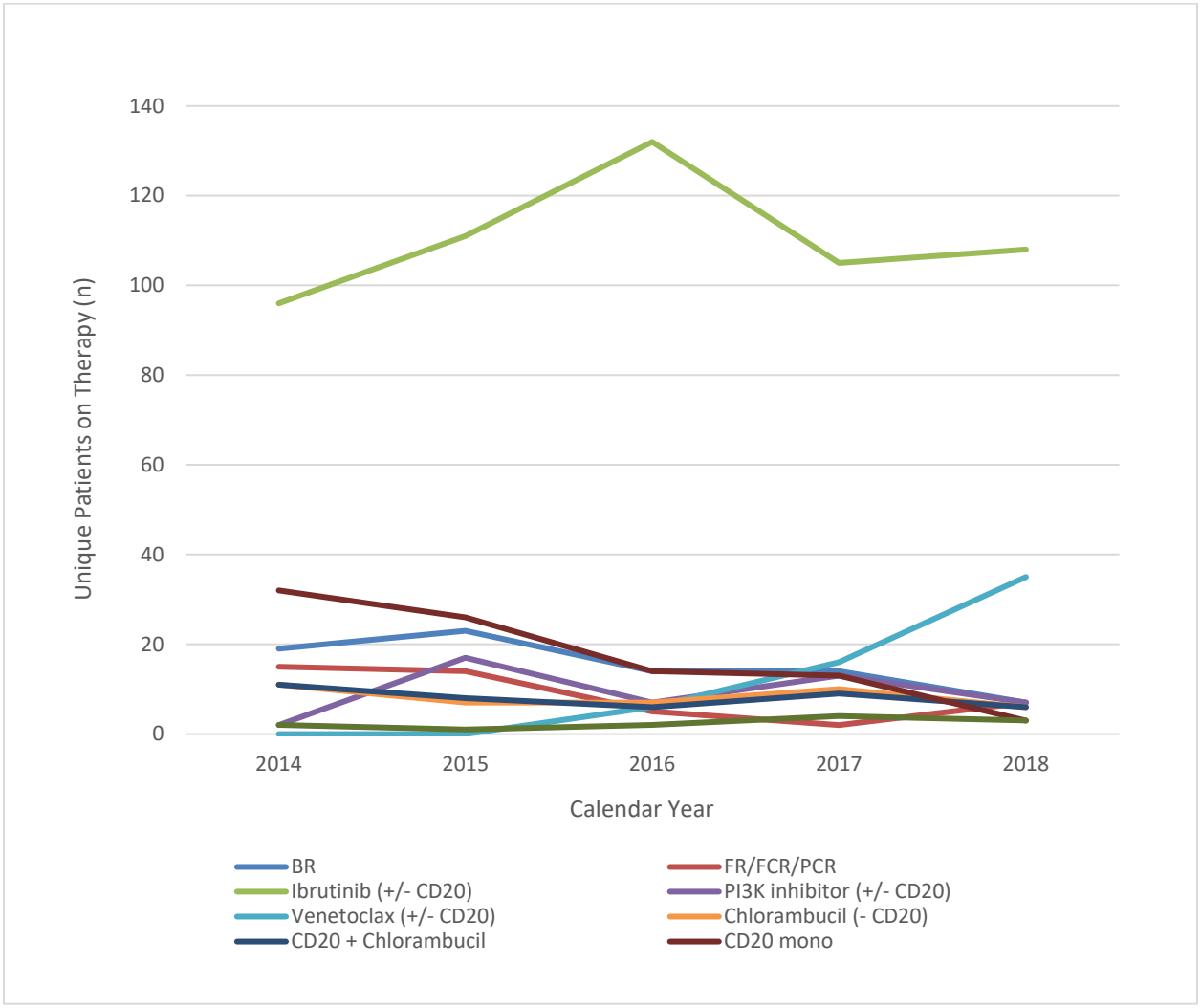
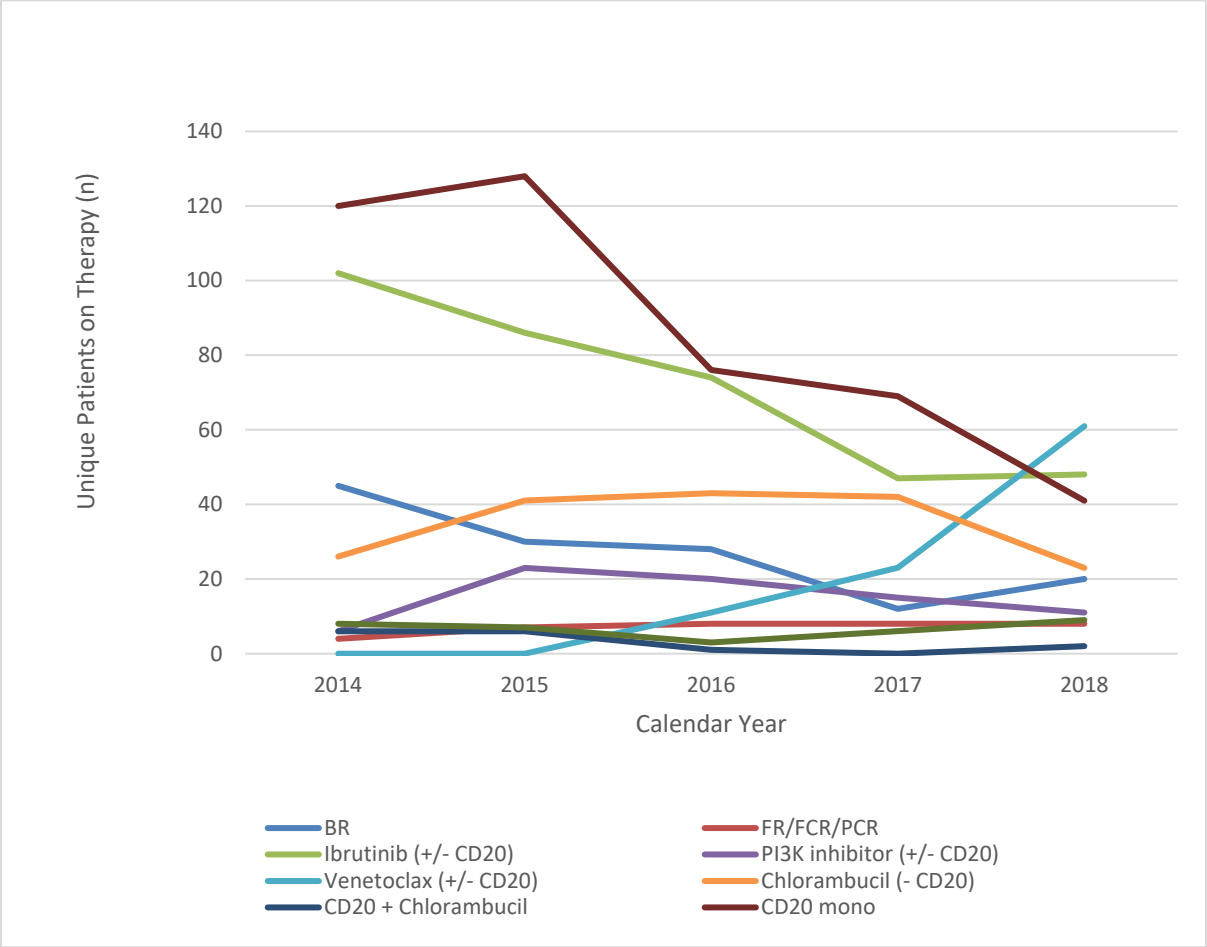


**Figure B3.** Yearly Uptake of Nine Select 3L+ CLL therapies 2014 -2018



**APPENDIX C**

**Table C1**. Overall Survival at 6 months post treatment initiation.

| Therapies | Survival in 6 months | P-value |
|---|---|---|
| BR | 164/167 (98%) | 0.464 |
| FR/FCR/PCR | 85/87(98%) | 0.7369 |
| IBRU | 160/165 (95%) | REF |
| PI3K | 4/4 (100%) | 1 |
| VEN | 2/2 (100%) | 1 |
| CHLOR | 120/121 (99%) | 0.199 |
| CD20+CHLOR | 50/50 (100%) | 0.593 |
| CD20 MONO | 31/31 (100%) | 1 |
| OTHER | 22/25 (88%) | 0.037 |
| CT/CIT | 472/481 (97%) | 0.052 |
| NA | 166/174 (98%) | |

## APPENDIX D

**Table D1.** Mean (range: Low and High)) Charlson Age score for patients alive and Dead at 6 months.

| ALIVE | BR | FR | CHLOR | CD20+ CHLOR | CD20 MONO | OTHER | IBRU | P13K | VEN | NA | CT/CIT | ALL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LOW | 1 | 1 | 1 | 3 | 3 | 1 | 1 | 2 | 6 | 1 | 1 | 1 |
| HIGH | 8 | 9 | 8 | 8 | 6 | 7 | 9 | 6 | 6 | 9 | 9 | 9 |
| MEAN | 4 | 4 | 5 | 5 | 5 | 4 | 5 | 4 | 6 | 5 | 4 | 5 |

| DEAD | BR | FR | CHLOR | CD20+ CHLOR | CD20 MONO | OTHER | IBRU | P13K | VEN | NA | CT/CIT | ALL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LOW | 1 | 2 | 3 | 4 | 3 | 3 | 3 | 5 | 5 | 3 | 1 | 1 |
| HIGH | 8 | 10 | 9 | 9 | 9 | 8 | 9 | 5 | 5 | 9 | 10 | 10 |
| MEAN | 5 | 5 | 5 | 6 | 6 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Table D2**. Charlson Age Score vs Survival times for NA and CT/CIT therapies

| **CCI Scores** | **CT/CIT** | | | **NA** | | | |
|---|---|---|---|---|---|---|---|
| | **N** | **OS1 [range]** | STDev | **N** | **OS1 [range]** | STDev | **P-value** |
| Overall | 153 | 782(9-1833) | 444 | 64 | 640(33-1652) | 434 | 0.031 |
| Low (1-3) | 28 | 829(176-1833) | 446 | 8 | 892(158-1500) | 552 | 0.7736 |
| Moderate-High (4-7) | 114 | 788(115-1739) | 443 | 50 | 607(51-1652 | 394 | 0.0106 |
| Very High (≥8) | 11 | 598(50-1200) | 399 | 6 | 576(33-797) | 256 | 0.8922 |

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# Vita

Oby Obodozie-Ofoegbu was born Grace Obiageri Onyenucheya Ekwu. She was born in Aba, a town in the industrious eastern part of Nigeria, to the royal family of Nathaniel and Florence Ekwu. She is the fifth of nine children, younger sister to Chiemeka Mgbokwere, His Royal Highness Walter Ekwu, Lolo Carol Okorie, Chief Ugochukwu Ekwu (deceased) and older sister to Chief Stanley Ekwu, Chief George Ekwu, Chief Charles Ekwu and Olive Nnadi (deceased). After graduating from St Michael's Girls' Primary School, Aba, Federal Government Girls College Owerri, and University of Ife, Ile-Ife, all in Nigeria, she moved to Trinity College Dublin for a Doctor of Philosophy in Pharmaceutical Sciences. Before moving to the United States, Oby was working as an R&D pharmacist in drug development and a college professor. She held several clinical, academic and administrative pharmacy and healthcare positions nationally and internationally. Oby decided to undertake a knowledge-gap bridging training in Clinical Research and translational science, to enable her engage in more patient-oriented and translational research career. This saw her pursue a PhD degree in Translational Science at the University of Austin, College of Pharmacy, graduating in May 2021. She is a minister of the gospel of our Lord and Savior Jesus Christ, the proud wife of Goodluck Izuora Ofoegbu and the proud mother of Prince Jideofor, Princess Mahogany, Prince Jamike, Princess Cleopatra and Prince Kossy Obodozie.

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